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ACTH

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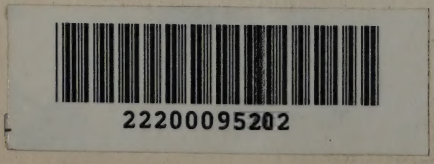
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INTRODUCTION

During the past three years or more the development of ACTH (Armour) has constituted, in our opinion, one of the greatest efforts in constructive team work in medical research that has occurred in peacetime in this country.

In the first place, the development of isolation and purification methods for ACTH (Armour) was dependent on team work on the part of the research personnel of The Armour Laboratories.

Secondly, the development of a practical animal bioassay method was accelerated by collaboration and cooperation between the research workers of The Armour Laboratories and Dr. George Sayers and his research associates.

In the third place, the study of ACTH (Armour) in the human beings required the active participation of many individuals in each clinical investigating unit in the various medical schools and teaching hospitals, because the adrenal glands are so concerned in so many metabolic processes that extensive studies were required on each patient to obtain the maximal information possible with the limited amount of hormone available at the time.

Finally, active collaboration and mutual understanding were required between The Armour Laboratories and the various investigative groups, as well as between research groups in different centers, in order that the exploration of the role of the adrenal gland in disease in general could be extended without undue hardship to any single group and, at the same time, avoid undue duplication of observations between different research units.

In summary, it is only by the active participation of many individuals, not only within given groups but between many different investigating groups and The Armour Laboratories, that it has been possible to make the progress that has been made thus far concerning the role of the adrenal gland in health and disease in the human being.

IMPORTANT

In view of the fact that adrenal cortical stimulation affects so many important metabolic and physiologic processes in the body, it is essential to become fully familiar with the metabolic and physiologic changes that may occur on adrenal cortical stimulation with ACTH. Likewise, dosage schedule should be considered in the light of the alterations that may occur.

SUMMARY OF THE DEVELOPMENT OF ACTH

The progress with respect to the effect of ACTH (Armour) in various disease syndromes was extremely rapid during 1949 and by the Fall of last year so much oral and lay press information and misinformation was about that The Armour Laboratories held a conference between all of the investigating groups using ACTH (Armour) on October 21 and 22, 1949, in order that results and information could be exchanged between the various groups. This conference revealed that the adrenal gland may be involved in a number of different disease syndromes, and it is the purpose of this paper to review the history of the development of the work with respect to ACTH (Armour.)

Historical

The history of the development of the knowledge of the role of the adrenal gland in health and disease and the role of ACTH (Armour) in stimulating the adrenal gland is indeed unique in medical annals. The reason for this statement is that it has required nearly one hundred years to arrive at a full realization of the role of the adrenal gland in a large group of human diseases and the possible implication that the adrenal gland may be important in human illness in general.

It is just over one hundred years ago that Thomas Addison first clasically described the disease syndrome which results from the destruction or non-function of the adrenal gland in the human being. Thus, he noted the pigmentation, asthenia, and anorexia characteristic of the syndrome, and was aware of the extreme ease with which these patients became suddenly and critically ill and, in fact, often died from minor infections and stresses of various types.

During the ensuing six decades the clinical syndrome was gradually clarified and the extreme inability of the Addisonian patient to withstand various environmental stresses such as infection, anorexia, exposure to extremes of heat and cold and to excesses of physical exertion, as well as to starvation, was observed and confirmed. However, it was not until two decades ago that the fundamental derangement in the electrolyte metabolism, with particular reference to sodium and potassium, was clarified and fully understood.

Likewise, during the first seventy-five years following Addison's description of the syndrome in human beings there was truly a vast amount of laboratory work done on animals. The majority of this work concerned the physiological results of removing the adrenal gland in animals, since the pituitary hormones were not known at that time. The investigations during this period clarified and confirmed that the adrenalectomized animal is, in most respects, the physiologic counterpart of Addisonian disease in the human being.

Twenty-five years ago Herbert Evans first reported that a pituitary extract prevented the atrophy of the adrenal gland which results from the removal of the pituitary gland in animals.

During the fifteen years succeeding Evans' report, considerable more work clarifying the physiologic and metabolic role of the adrenal gland in animals was done, including the use of pituitary fractions, but little precise work was done because there were no really quantitative bioassay methods available to allow an accurate determination of the ACTH potency of pituitary gland fractions then available.

Nonetheless, during this period techniques were evolved to reveal that it is the adrenal gland that allows the animal and the human being to withstand the large variety of environmental stresses. However, the full implications of this phenomenon in human disease in general were not discerned.

Bioassay of ACTH (Armour)

It was not until the development of a quantitative bioassay method for ACTH was achieved by Sayers and Sayers eight years ago that it was possible for the biochemist to undertake more precise chemical fractionating procedures. Likewise, it was not until then that it was possible for physiologists to study the effect of ACTH stimulation of the adrenal gland in animals with any degree of accuracy because of a wide variation in the potency of the hormone preparations that were previously available.

The Armour Laboratories first started working on ACTH (Armour) twelve years ago in collaboration with Dr. J. B. Collip of McGill University under the then considerable bioassay handicaps. However, little progress was made until the Sayers and Sayers bioassay technique became available, and even then, considerable more work was required in The Armour Laboratories to achieve more practical methods for performing the bioassay.

Having accomplished these ends six years ago, our Research Department began working diligently; first under Dr. F. C. Koch and later under Dr. E. E. Hays, on the isolation and purification of ACTH (Armour), but it was not until three years ago that the hormone was produced in adequate quantities of a potency and purity satisfactory for use in human beings. Since then, substantial contributions were made and progress achieved by The Armour Laboratories' pituitary research team consisting of J. D. Fisher, L. Walaszek, J. Kocsis, I. M. Bunding, R. E. Thompson and J. B. Lesh.

Clinical use of ACTH (Armour). Fundamental Observations

Three years ago Dr. George Thorn first injected ACTH (Armour) in human beings and determined by laboratory observations that the hormone stimulated the adrenal gland. Thus, he reported (1) (2) (3) (4) (5) that the injection of large doses of ACTH (Armour) causes a marked drop in the number of cir-

culating eosinophils in the peripheral blood and causes an increase in the uric acid-creatinine ratio in the urine. Likewise, he reported that the administration of ACTH (Armour) causes an increased urinary excretion of 17-ketosteroids and 11-oxysteroids, which are some of the metabolic products of adrenal corticoids. Furthermore, he observed that the administration of large doses of the hormone causes retention of sodium and chloride and results in an increase in the excretion of potassium and nitrogen in the urine of normal human beings.

During the succeeding two years the hormone was used extensively experimentally in both normal human beings and human beings with obvious endocrine defects to ascertain the physiologic and metabolic effect of stimulating the adrenal gland in these situations.

During this period of time Thorn's observations were confirmed by many investigators using large doses of the hormone and were extended with particular reference to calcium and phosphorus metabolism by Fuller Albright (6) and his colleagues, and were further extended with regard to the effect of adrenal gland stimulation on carbohydrate metabolism by Conn, (7) (8) (9) and Browne, (6), Sayers and Burns, (10), and McQuarrie.

Paralleling the fifteen-year period of refinement of bioassay and fractionating techniques following Evans' work there was, of course, an extensive amount of laboratory work done on both animals and human beings, using newer techniques, to ascertain by objective means the role of the adrenal gland in physiology and metabolism, to the end that a number of hypotheses were developed concerning the role of the adrenal gland in stress situations.

The Alarm Reaction and Adrenal Exhaustion Phenomenon

Thus, it was determined that it is the adrenal gland that allows the animal or human being to withstand acute environmental stresses of almost any type, such as trauma, infections, burns, starvation, exposures to extremes of heat or cold and extremes of physical exertion, to name a few. It was further learned that these stress situations were associated with laboratory evidence of endogenous adrenal gland stimulation along the lines noted above.

These observations, with others noted above, in both animals and human beings gave rise to the hypothesis that the ability to withstand acute environmental stresses is the result of a sudden and marked endogenous ACTH stimulation of the adrenal gland which is called, in physiological terms, the "alarm reaction."

On the other hand, it was observed by many investigators that neither animals nor human beings can withstand severe stresses indefinitely, and it was later determined that during the "post alarm reaction" period of inability to withstand further stresses, there is laboratory evidence that adrenal gland function has decreased. These observations gave rise to the

concept of the "adrenal exhaustion phenomenon."

Thus, a patient may be in excellent clinical condition for hours or even several days after major surgery following which the patient may go into shock and possibly die. Likewise, the traumatic or burn case may remain in extraordinarily good condition for a period of hours or even days before he goes into shock, if this should occur.

Examples are the rather common observation that a severely burned individual may return to a fire to help others to escape and even help get a fire under control before the person in question becomes aware of the extent of his own burns, although he may later collapse and die. Likewise, severely injured individuals may help others from accidents with little consideration or knowledge of their own condition, although they may later go into shock and even die.

All of these are simply clinical examples of the "alarm reaction" and the "adrenal exhaustion phenomenon" and are clinical confirmations of the fact that it is the adrenal gland that allows the body to withstand stresses. On the other hand, when the adrenal gland does not function at the high level of activity commonly associated with the "alarm reaction" or does not continue to function at a high level of activity during continued stress, the prognosis of the patient may be poor. Contrariwise, continued over-activity of the adrenal gland may likewise affect the prognosis of a case in question.

In view of the fact that there is objective laboratory evidence that the adrenal glands secrete lesser amounts of adrenal cortical hormones during the "adrenal exhaustion" period under continued stress, as well as the fact that the adrenal cortical hormones are extremely complicated chemical compounds, the hypothesis was evolved that the adrenal gland simply could not continue to synthesize and secrete these chemically complex adrenal cortical hormones over any extended period of time.

More recent studies of Thorn, et al, (6) concerning adrenal cortical functional reserve in the postoperative state during the "adrenal exhaustion" period using ACTH (Armour) for testing the adrenal cortical functional reserve do not confirm this hypothesis. The reason for saying this is that the injection of ACTH (Armour) during the "adrenal exhaustion" period reveals that the adrenal gland is quite capable of stimulation in most cases during this period, although a large dose of ACTH (Armour) may be required in some cases.

In other words, the inability to withstand continued stress may not lie so much in the inability of the adrenal glands to continue to secrete adrenal cortical hormones, but rather in the fact that under prolonged stress, endogenous secretion of ACTH may not continue at a level adequate to stimulate the adrenal gland to any marked extent. It remains to be determined whether this defect lies in the inability of the pituitary gland to continue to secrete ACTH under prolonged stress, or results from the decreased stimulation of the pituitary gland to secrete ACTH in continued stress situations.

Adaptation Phenomenon and Adaptation Diseases

Selye, in doing repeated stress experiments in animals under different controlled experimental conditions, noted the development of various abnormal physiologic states and brought forth the hypothesis of the "adrenal gland adaptation phenomenon" and "adaptation disease." Thus, he concluded that certain types of experimental hypertension, nephritis, and joint disease which occur in chronically stressed animals under different experimental conditions are the result of the adaptation of the adrenal gland to chronic internal and external environmental stress situations.

All of this work, however, on the basis of present knowledge in the human subject, is a far cry from an explanation of the occurrence of a large group of diseases in the human being, because with the methods available to date, there is no objective evidence that this large group of human diseases is the result of, or is associated with, chronic stress situations, as these may be reflected in altered or abnormal adrenal cortical function. It is in part for these reasons that the use of ACTH (Armour) was limited largely to the study of human beings with obvious endocrine abnormalities during the first two years of its availability.

First Observations on Effect of ACTH (Armour) on Disease Syndromes

Nonetheless, during this first two-year period of ACTH (Armour) availability there were three diseases whose courses were altered by administration of ACTH (Armour). Soffer, (11) in 1948, reported that the administration of 100 mg. of ACTH (Armour) a day to a myasthenia case with a thymic tumor, over a 5-day period, resulted in a decrease in the size of the tumor during the period of hormone administration, with no effect on the myasthenia during the study period. However, there was a progressive improvement in myasthenia gravis symptoms following the cessation of the hormone administration. Wolf and Torda (12) have confirmed Soffer's results with respect to the improvement of myasthenia gravis cases after 5-day treatment periods of ACTH (Armour). It is obvious that considerable work will be required to arrive at a rational interpretation of the results and elucidate the mechanism of this syndrome.

Conn (13) later reported that the administration of ACTH (Armour) to acute gouty arthritics caused a complete remission of the symptoms in a matter of hours, although the symptoms returned in some cases several days following cessation of ACTH (Armour) administration. Wolfson (14) has confirmed Conn's results and has further reported that concurrent administration of colchicine with ACTH (Armour) in cases that could not be controlled by colchicine alone, caused a complete remission which could be maintained on continued administration of non-toxic doses of colchicine alone in most cases. Wolfson administered 50 mg. doses at 6-hour intervals until an essentially complete remission was obtained, which normally

occurs in 6 to 18 hours. Margolis and Kaplan (19) and others have confirmed Wolfson's results.

Farnsworth (6) administered ACTH (Armour) to nephrotic children, in whom she noted a continued retention of fluids during administration of the hormone at a level of 100 mg. a day. However, a marked diuresis occurred following cessation of ACTH (Armour), in most cases not only of the fluids retained under ACTH (Armour) administration, but the previously accumulated fluids as well. She has further reported that some of the cases have gone into a complete remission with a reversal of albumin-globulin ratio toward normal levels as well as blood cholesterol in the same direction, and in some cases a complete disappearance of albuminuria. In later studies on younger children it has been observed that diuresis may occur while the patient is still on ACTH. The effect of ACTH (Armour) has varied widely from no effect to a complete remission and, likewise, the duration of the remission has varied from rapid reaccumulation of fluids immediately following diuresis to complete remissions of some months' duration. These results have been confirmed by Riley, Janeway, and others. Here again it is obvious that considerable work will be required to clarify the basic mechanisms in this disease syndrome, but in the interval, ACTH is a means of controlling nephrosis in many cases.

In all of the above syndromes it has been hypothesized by some investigators that metabolic defects of one type or another may be the cause of the disease which accounts for their exploration during the first two-year period of ACTH (Armour) availability. Nonetheless, during this period the full implications of adrenal gland function in disease states in general were not visualized or comprehended.

The Effect of ACTH (Armour) in Collagen Diseases

It remained for the dogged Dr. Hench and his colleagues (15) at the Mayo Clinic to use ACTH (Armour) in rheumatoid arthritis with the now well-established striking results. Thus, in a bed-ridden, completely incapacitated arthritic, the pain may almost or completely disappear within 24 hours after the first injection of ACTH (Armour). In a matter of two to three days, the swelling may be almost or completely gone, and mobility may return as close to normal as previously existing bony deformity will allow. Equally striking is the sense of well being, increased muscle strength and increased appetite. Likewise, the red blood cell sedimentation rate returns to the normal range within 6 to 12 days. In summary, there is a rapid and dramatic remission accomplished in a matter of days when the adrenal gland of the arthritic patient is stimulated with ACTH (Armour). The early studies were done at high dosage levels of ACTH (100 mg. daily) since the aim was maximal adrenal cortical stimulation and the physiologic and metabolic effects of over-stimulation were observed. It is now known, however, that these excessive doses are not required and that most patients can be put into a complete clinical and laboratory remission at doses of ACTH (Armour) (40 - 50 mg. daily) which cause only slight or non-detectable physiologic and metabolic shifts.

It is also now known that most patients can be maintained in a remission on doses of the order of 10 to 30 mg. daily.

In view of the fact that it was difficult to rationalize why such widely divergent diseases such as myasthenia gravis, gouty arthritis, nephrosis, and rheumatoid arthritis should be affected by adrenal gland stimulation, it was early decided to keep the studies on a broad base and screen disease syndromes in general to ascertain the role of the adrenal gland in human illness in general.

The first and obvious extension in these studies was to the collagen diseases in general. Thus, Massel, et al, (6) and his colleagues reported that there was a rapid disappearance of the fever, percarditis, myocarditis, arthritis, and pleuritis in acute rheumatic fever when relatively low doses of ACTH (Armour) (30 - 50 mg. daily) were administered. Likewise, electrocardiographic changes returned toward the normal. Furthermore, the red blood cell sedimentation rate returned to normal in a matter of ten days to two weeks. In other words, a rapid remission was obtained without evidence of the severe residual heart disease commonly observed in this type of case. They further reported that the cases studied remained in a clinical and laboratory remission after cessation of the hormone administration without demonstrable heart disease from the attack in question. It should be pointed out, however, that considerable time must pass before it can be stated clearly that damage to the heart muscle was completely obviated and the permanent valvular damage has been circumvented, since it is well known that rheumatic heart disease may develop gradually without clinical evidence of active disease. The final assessment of the results will require considerable more confirmation and extension of the above results as well as passage of time. Nonetheless, in the interval, the results are sufficiently clear-cut to indicate the use of ACTH in early acute cases of rheumatic fever.

The results in cases of chronic progressive rheumatic fever reported by Massel, et al, were in many respects quite as striking as in the case of acute rheumatic fever except that the heart size did not return to normal and the valvular disease did not disappear although a marked improvement, both clinical and laboratory, was attained during the period of ACTH (Armour) administration. Unlike the acute rheumatic fever cases, and more like rheumatoid arthritis, the active disease returns when ACTH (Armour) administration is stopped.

In addition to these two diseases of the collagen disease group, ACTH (Armour) has been used with equally striking results in lupus erythematosus disseminatus by Thorn, Howard and Harvey, Elkinton and Hollander, Bauer, Ragan, and Baehr. In most cases a complete remission was obtained under ACTH (Armour) administration and many have remained in remission for some time after cessation of the hormone administration. However, some cases have relapsed immediately on stopping the hormone or on lowering the dose below the minimal effective maintenance level for the patient in question. It is interesting that larger doses of ACTH (Armour) (100 mg. daily) are required in lupus cases, as a group, than in the other collagen diseases.

Ragan, (6) Stokes, (6) Milhorat, (6) and Farber (6) have reported either a temporary or even prolonged remission of dermatomyositis resulting from the administration of ACTH (Armour) although again some cases appear to require continued administration of the hormone to maintain a remission.

Bayles and Stillman, (6) and Howard and Harvey (6) have reported an improvement in early cases of scleroderma during ACTH (Armour) administration, but noted little effect on long-standing cases where collagen deposition is both long-standing and extensive. Again, in this syndrome, most of the cases require continued administration of the hormone and it appears to be of value only in early or acute cases.

Finally, Bassett, (6) Elkinton and Hollander (6) and Ragan (6) have reported a complete clinical and laboratory remission in periarteritis nodosum during the period of ACTH (Armour) administration. Here again, some cases have remained in remission for some time following cessation of the hormone administration, whereas others have relapsed promptly when the hormone is stopped, although some of these cases have been maintained in remission by continued administration of the hormone.

From the knowledge available today concerning this collagen disease group it is clear that it will take considerable more investigation at the fundamental level before the mechanism of these diseases is understood, but in the interval for the first time there appears to be an effective means for treating this commonly occurring group of disabling and even fatal group of diseases with essentially no risk to the otherwise disabled patient.

Another reason for keeping the studies on a broad base with regard to the role of the adrenal gland in various disease syndromes, is the fact that there is no objective laboratory evidence to date that indicates that the adrenal glands function differently in individuals who have one of the above diseases than they do in normal human beings. This, of course, may be the result of as yet inadequate laboratory techniques, but it occurred to us that possibly other diseases may be the result of what we should like to call "adrenal mal-adaptation" to chronic internal or external environmental stresses which cannot be measured by the techniques available to date.

As noted above, Farnsworth has reported on the effect of ACTH (Armour) in nephrosis. She later reported (6) a rapid decrease in albuminuria and return of the blood chemistry toward normal levels and a marked increase in kidney function in acute and sub-acute glomerular nephritis when ACTH (Armour) is administered. Glomerular nephritis is, however, so variable in its course and so unpredictable in its outcome that considerable more work will be required to confirm and amplify these observations and to arrive at any possible mechanisms relating thereto. Work in this field should not be undertaken without extensive facilities since the damaged kidney may not be able to excrete any retained electrolytes or fluid.

Effect of ACTH (Armour) on Congenital Hypoglycemia

McQuarrie and his colleagues have reported that the administration of ACTH (Armour) to infants and children having severe hypoglycemia accompanied by convulsions blocked the hypoglycemic syndrome and after intensive metabolic study periods on doses varying from 18 to 40 mg. a day, the fasting blood sugar levels were maintained above the hypoglycemic levels by injection of 10 mg. of ACTH (Armour) two to three times weekly.

These investigators conclude that ACTH (Armour) is to the hypoglycemic what insulin is to the diabetic and express the opinion that there may be a really effective treatment of congenital hypoglycemia by adequate doses of ACTH (Armour.)

ACTH (Armour) and Ulcerative Colitis

Bauer (6) and Randolph (6) have reported a rapid and decided clinical improvement in chronic ulcerative colitis under ACTH (Armour) administration. Thus, the diarrhea may stop within 48 to 72 hours and the mucus and blood may rapidly decrease in the stools. The appetite increases rapidly, and patients gain weight, and the general outlook is improved. The pathologic changes in the mucosa are, however, much slower in improving and disproportionately less than the improvement with the clinical course. The early studies were done in long-standing cases with high doses of ACTH (100 mg. daily) but later studies on earlier cases on smaller doses (50 mg. daily) are more encouraging and a number of these cases have remained in remission.

ACTH (Armour) in Hypersensitivity States

Randolph (6) has reported that the administration of ACTH (Armour) causes a rapid disappearance of severe asthma or status asthmaticus, which may last for a matter of days to several weeks or longer following cessation of ACTH (Armour) treatment (100 mg. daily for two days). He also reported that the administration of ACTH (Armour) causes a dramatic disappearance of all of the symptoms of hay fever in a matter of a few hours to 24 hours or more. He further reported that the hormone administration "blocked" the hypersensitivity phenomenon on further exposure to the allergin. Finally, he reported that the administration of ACTH (Armour) caused a dramatic healing of eczematous lesions of known allergic etiology. In both of these latter situations improvement continued for a matter of days or weeks or longer subsequent to the cessation of the hormone administration.

Howard, et al, (6) almost concurrently confirmed Randolph's observations in asthma, but they gave 50 mg. of ACTH (Armour) daily for ten to fourteen days in less severe cases and a tapering dose beginning with 100 mg. daily and decreasing the dose over a ten-day period in more severe cases. They, furthermore, reported rapid disappearance of nasal polyps in asthmatic subjects under ACTH (Armour) administration. Howard, et al, likewise reported that ACTH (Armour) administration (100 mg. daily) resulted in a rapid disappearance of fulminating symptoms and signs of penicillin and sulfonamide sensitivity. In the latter, the symptoms and signs did not return on cessation of the hormone administration after five to seven days therapy in the cases studied. The use of ACTH should certainly be considered in any case of drug sensitivity.

Howard, et al (6) have also reported a very rapid disappearance of the lesions of pemphigus and exfoliative dermatitis during the period of ACTH (Armour) administration. In some cases a remission was maintained for some time following the cessation of the hormone administration, whereas in others the disease relapses promptly. Ragan has confirmed Howard's observations in pemphigus.

These observations are at such a fundamental level in an understanding of the mechanism of antigen-antibody reactions and the role of adrenal corticoids on the tissue reaction to sensitivity, that it is extremely important to confirm and pursue these observations in the hypersensitivity states. This is particularly true since the animal laboratory work is, to say the least, counter to the results observed in human beings. On the other hand, in the interval, there is an effective means for controlling severe allergic states.

ACTH (Armour) in Infectious Diseases

In view of the observations in the allergic states, it was decided to explore the role of the adrenal gland in frank infectious diseases, since these are the most clear-cut situations involving the antigen-antibody phenomena and may result in clues to the best approach to the more obscure tissue reactions.

Finland (6) has reported on the results of the administration of ACTH (Armour) in lobar pneumonia where no antibiotics were concurrently administered. He reported that in a matter of hours following administration of ACTH (Armour) in this disease, the temperature fell by crisis, the patient became clinically and dramatically improved in 12 to 24 hours, and that the symptoms and signs were almost gone in a matter of 24 to 36 hours. Most spectacular was that this occurred in spite of a positive blood culture in one case for 36 hours after the beginning of ACTH (Armour) administration. After tapering off the dose after a five-day period, the patients were left essentially and completely clinically well. In one case of atypical, viral pneumonia, Finland reported a rapid regression of symptoms and signs during ACTH (Armour) administration, but these returned on stopping the therapy. Interestingly enough, the measurable anti-bodies appeared at the usual time.

Again, it must be emphasized that these observations are very preliminary, but they are so extremely fundamental that it is of the greatest academic as well as practical importance to pursue these studies since these observations give the first rational clues to an understanding of the epidemiology of infectious diseases.

Stokes and his colleagues (6) have present preliminary data on administering ACTH (Armour) in cases of sub-acute viral hepatitis in which there was a return of liver function, blood proteins and other deranged metabolic phenomena toward the normal in a matter of several weeks in cases that had had active disease for a matter of months.

Coriall, et al, (6) undertook a preliminary experiment on the effect of ACTH (Armour) in poliomyelitis, but in this disease an analysis of the results failed to reveal any effect of adrenal gland stimulation on either the severity or course of this infection.

Freeman (6) has reported on the use of ACTH (Armour) in pulmonary tuberculosis and, although there was a preliminary rapid clearing of the lesions and a sense of well-being, as well as disappearance of exhaustion and toxicity, there was a spread of the infection during ACTH (Armour) administration which may be accounted for in part by the rather well-known inability of the human body to cope with the tubercle bacillus.

In the light of the results in bacterial and viral infectious diseases, it is clear that this area of disease must be explored in considerable detail in order to arrive at a sound hypothesis concerning the occurrence of these infectious diseases, as well as to explore the mechanisms by which tissues are capable of dealing with infectious agents. This group of diseases, together with the hypersensitivity phenomena, require thorough exploration because they may reveal clues concerning the possible mechanisms in some of the more obscure diseases discussed above. Furthermore, studies in this field may allow a more rational interpretation of epidemiology as well as reveal clues as to the true etiology and therapy of many diseases. On the other hand, it should be emphasized that ACTH (Armour) should not be considered a therapeutic agent in infectious diseases.

ACTH (Armour) in the Lymphomas and Leukemias

During the past year, Pearson, Rawson, et al (16) reported a marked regression of the lesions of chronic lymphatic leukemia, lymphosarcoma, and Hodgkin's diseases during ACTH (Armour) stimulation of the adrenal glands, with little or no change in the histopathology of the lymph nodes or bone marrow of the cases studied. As is the case with many of the other syndromes, the lesions returned when the hormone administration was stopped. The effect of long continued administration of ACTH (Armour) in these lymphomas has not been reported.

Later, Farber, et al, (6) and Pearson, Rawson et al, (17) reported

that the administration of ACTH (Armour) in some cases of acute lymphatic leukemia resulted in a complete remission with both the peripheral blood and the bone marrow returning to normal in about half of the cases treated. However, the disease relapses in all cases either while still receiving ACTH (Armour) or after a variable but short time after therapy is stopped. ACTH (Armour) should not be considered a therapeutic agent in the treatment of lymphomas and leukemias, although it is an unsurpassed investigative toolto explore the mechanism by which tissue cells escape their normal invironment.

ACTH (Armour) in Acute Inflammatory Diseases of the Eye

More recently, McLean and Gordon (18) and Smith, Whitney, et al, have reported a rapid regression of acute inflammatory diseases of the eye, with particular reference to acute iritis and acute chorioiditis and uveitis on ACTH (Armour) administration. In the cases studied which, on the basis of past experience would likely result in eventual blindness, there was a very rapid return of the eye toward the normal status under ACTH (Armour) administration. Most of the cases studied shortly after the onset of the disease have remained in remission up to date after cessation of ACTH (Armour) administration, whereas in the longer duration cases there has been a return of the acute inflammatory diseases upon stopping ACTH (Armour) administration, although this type of case can be maintained in remission on continued ACTH (Armour) administration.

There are a number of additional studies in progress covering a wide variety of disease syndromes which are aimed at clarifying and defining the role of the adrenal gland in human illness in general. It is yet too early to speak of the results, but it can be said that the area of diseases affected by ACTH (Armour) stimulation of the adrenal gland is even broader than those outlined above.

The Adrenal Gland in Mental Diseases

To emphasize the magnitude of the problem concerning the role of the adrenal gland in human disease, it should be noted there is accumulating evidence of adrenal gland "malfunction" in various types of mental disease. However, this area of medicine is so complex and so relatively unexplored, and the investigative techniques are so crude, that it is obvious that it will take a considerable amount of work and time to clarify the issues.

Summary

In summary, the picture that appears to be developing is that the adrenal gland plays perhaps the largest single role in determining whether a person is sick or well, regardless of the illness or the cause thereof. In the light of these facts, it is extremely important to continue the studies at the fundamental level in order that we may eventually understand human illness.

At this point, it should be emphasized that the above is not meant to indicate that stimulation of the adrenal gland will make all disease syndromes better, since there is evidence accumulating that adrenal cortical over-activity may, in fact, aggravate some disease syndromes and this may apply particularly to hypertension and some mental states.

On the basis of information to date, it appears that the person with adrenal glands that can adequately react to various types of stresses, be these trauma, infection, emotion, or an almost infinite variety of other types of internal and external environmental stresses, may remain well, whereas the person with "hypofunctioning," "malfunctioning," "malstimulated," or even "hyperfunctioning" adrenal glands, or whose tissues are insensitive or over-reactive to mechanisms activated or inhibited by adrenal gland stimulation, may eventually come down with any one or more of an almost unlimited variety of diseases.

It is in the light of results to date and a forecast into the future that it appears that the comprehension of the role of the adrenal gland in health and disease in human beings has probably opened up the largest single area of medicine that has occurred since the discovery of bacteria.

It may take decades to work out all of the details as to the true cause and prevention of the numerous diseases which afflict a substantial proportion of the population of the world today, but when these are accomplished a new type of medical research, a new type of medical teaching, and a new type of medical therapeutics may be evolved. However, in the interval, the available facts indicate that ACTH (Armour) is an effective therapeutic agent in controlling a number of serious and disabilitative disease syndromes.

Footnote — All of the studies referred to in this manuscript were reported in preliminary form at the First Clinical ACTH Conference held in Chicago, October 21 and 22, 1949, under the auspices of Armour and Company and since published by Blakiston and Company of Philadelphia, Pennsylvania, U. S. A.

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METABOLIC AND PHYSIOLOGIC EFFECTS OF ADRENAL CORTICAL STIMULATION

THE ALARM REACTION

There is a phenomenon that occurs in the body when the animal or human being is exposed to an acute "stress" situation, such as fear, anger, trauma, etc., which is called the "alarm reaction" which results from the sudden stimulation of the adrenal medulla by the parasympathetic nervous system to secrete large quantities of epinephrine. Thus, in these "stress" situations the individual becomes more alert, the carbohydrate reserves of the body are mobilized as a source of energy, muscular strength is markedly increased, the pupils dilate for better sight, and peripheral blood vessels contract to minimize potential bleeding, the blood pressure rises - perhaps to increase cerebral blood circulation, and sweating increases to compensate for the increased heat produced by the higher energy turnover, all of which are desirable in acute "stress" situations.

This course of events cannot go along for long, however, and the body energy reserves must be mobilized and replenished. This is accomplished by the stimulation of the pituitary gland to put out ACTH which, in turn, stimulates the adrenal cortex to put out adrenocortical hormones.

It is these adrenocorticoids that counterbalance the effects of the first phase of acute "stress" situations or the "alarm reaction" and replenish energy stores to render the body capable of reacting adequately physiologically to continued "stress" situations of the above types as well as others, such as trauma, surgery, infection, burns and the such.

METABOLIC EFFECTS OF ADRENAL CORTICAL HORMONES

When the adrenal gland is stimulated, three general types of cortical hormones or corticoids are secreted; namely,

1. Compound F-like hormones, or 17-Hydroxycorticosterone-like steroids.

The evidence indicates that the human adrenal cortex secretes Compound F-like hormones or 17-hydroxycorticosterone-like hormones, and not Compound E which is secreted only in trace amounts if at all. Furthermore, the adrenal cortex secretes many times more of these types of hormones than the others that will be discussed below.

This group of adrenal hormones cause glyconeogenesis or conversion of glucose to glycogen in the liver and muscles to restore the glycogen stores that are used up in the "alarm reaction," or reaction to acute "stress" situations.

They also mobilize fat from the fat depots as a source of energy and possibly for conversion to glucose and glycogen.

Likewise this group of steroids mobilize amino acids from the tissue proteins, partly as a source of energy, partly for conversion to glucose and glycogen, and partly to make amino acids available for protein synthesis in wounded or abnormal tissues.

The action of maximal adrenal cortical stimulation by large doses of ACTH or high concentrations of this group of hormones is reflected in:

a) Increased excretion of nitrogen
b) Increased excretion of potassium
c) Increased excretion of phosphate
d) Increased excretion of calcium

All of the above are a reflection of mobilization of protein stores and the increased excretion of potassium and phosphate particularly, as well as nitrogen, indicate a loss or shift of protein in the tissues. When this is carried too far or stimulation is too great renal glycosuria or even hyperglycemia may result since glyconeogenesis may not occur as rapidly as sources of energy are mobilized and converted to glucose.

The increased utilization of fat, both for energy and conversion to glucose, is reflected by a decreased respiratory quotient and the changes in the metabolic pathways of fat, as reflected by a lack of ketonemia and a lack of ketonuria, as well as the absence of acidosis, in the face of a decreased respiratory quotient which is an indication of the utilization of fat as a source of energy.

There are balancing mechanisms that may come into operation to prevent excessive metabolic shifts - and the increased nitrogen excretion, weight loss, and glycosuria, if it occurs, may disappear on a given dose of ACTH. In any case, this is seldom a serious problem even on high doses of ACTH, and is rarely a matter of concern on therapeutically effective doses.

In summary, the main metabolic action of this group of the 17-hydroxycorticosterone-like steroids is in mobilization of sources of energy and restoring sources of energy in the form of glycogen in the body. It is important in considering this group of steroids and their action, that the hyperglycemia and glycosuria is not indicative of diabetes, but simply is due to too rapid mobilization of energy sources. It is also important to realize that glycosuria and hyperglycemia are not commonly observed on ACTH stimulation; that it occurs only on high doses of ACTH; that it is not a true diabetes; and that it disappears when the dose is lowered, or when the administration of the hormone is stopped.

2. Desoxycorticosterone-like hormones.

Desoxycorticosterone-like steroids cause retention of sodium and chloride with concurrent retention of fluids and decreased sweating.

This group of hormones also cause an increased excretion of potassium which may result to some extent from the displacement of intracellular potassium by retained sodium as well as from the breakdown of intracellular proteins.

When the adrenal gland is stimulated maximally or excessively the development of edema may occur as a consequence of retention of too much sodium, chloride and fluids. Likewise, potassium deficiency may occur from overexcretion of this ion which may be reflected by fatigue and electrocardiographic changes characteristic of potassium deficiency.

Fortunately, however, there are compensating mechanisms which may come into operation on continued adrenal cortical stimulation with the result that most individuals will diurese retained fluids and sodium and chloride, and will begin to retain potassium while still on the same dose of ACTH or when the dose is decreased. This compensating mechanism may be the result of inhibition of the secretion of this type of corticoid as a consequence of too high blood levels of desoxy-like cortoids, although there is some evidence that the adrenal cortex can secrete corticoids that actually cause excretion of sodium and chloride and retention of potassium. The possibility of course also exists that the tissues of the body will become non-reactive to these steroids beyond a certain degree of electrolyte imbalance and equilibrium may be reached through this means. This electrolyte effect and resulting edema is not serious at therapeutically effective doses in most cases, and even when it occurs as it may on large doses of ACTH, it can be easily overcome by either administering a diuretic, lowering the dose, or omitting several doses to allow diuresis to occur. This electrolyte effect can be further minimized by putting the patient on a low salt, high potassium intake.

The Compound F-like or 17-hydroxycorticosterone-like hormones also have an electrolyte effect similar to the above but the effect of these hormones on electrolytes is minimal compared to the desoxycorticosterone-like hormones. On the other hand, the desoxycorticosterone-like hormones have none of the metabolic or physiologic effects characteristic of the Compound F or 17-hydroxycorticosterone-like hormones.

3. Adrenal androgens.

The third group of steroids produced by the adrenal gland are androgenic and anabolic in character, and may be a balancing mechanism against the protein catabolic effect of the Compound F-like or 17-hydroxycorticosterone-like group of steroids.

In addition, this group of steroids, the corticoandrogens, when secreted or administered in too great a quantity, particularly in females, may cause masculinization, hirsutism, and amenorrhea. However, these effects are the result of excessive stimulation of the gland or an inherent defect in the adrenal gland which results in preponderant secretion of the androgen-like steroids. ACTH stimulation of the adrenal gland at therapeutically effective levels in most diseases and cases is seldom accompanied by evidence of excessive adrenal androgen secretion. However, as a general principle, the dose should be kept as low as possible consistent with a therapeutic effect to circumvent this possibility, especially in women and children.

The Compound F-like or 17-hydroxycorticosterone-like hormones may have these same effects in large doses and some investigators believe these androgenic effects may be the result of excessive secretion of these types of hormones by the adrenal gland because highly active androgens have not been isolated from the adrenal gland. However, the evidence is in favor of the adrenal gland secreting androgens because large quantities of androgenic breakdown products (17-Hydroxy-iso-androsterone) are excreted in the urine when the adrenal gland is stimulated.

METABOLIC DEGRADATION PRODUCTS OF ADRENAL CORTICOIDS

The best correlation between the degree of adrenal cortical stimulation and metabolic effect is the degree in the increase in the urinary excretion of 17-keto-steroids and the 11-oxy-steroids. The 17-keto-steroids appear to be the metabolic degradation products of the adrenal androgens and some of the 17-hydroxycorticosterone-like steroids. The 11-oxy-steroids appear to be some of the degradation products of the 11-oxy and 17-hydroxy-like corticoids.

In summary, the important thing to remember with respect to ACTH stimulation of the adrenal gland is that every attempt should be made to work at a dosage level below that which causes any of the above effects and this can be done in the treatment of many patients with most diseases.

PHYSIOLOGICAL EFFECTS OF ADRENAL CORTICAL STIMULATION

In addition to the above metabolic effects, there are a number of physiological effects which in so far as can be determined, are not part and parcel of the above metabolic changes. Most of these physiological changes, in so far as can be determined, however, appear to be a function of the action 17-hydroxycorticosterone-like steroids.

1. The effects on the hemopoietic system.

Adrenal cortical stimulation has a profound and marked effect on the entire hemopoietic system.

a) Eosinophiles

The most sensitive test of adrenal cortical stimulation is the eosinophil count in the peripheral blood. This decreases markedly when ACTH is administered and is a rough and ready guide of adequate ACTH stimulation. Generally, there is very little, if any, change in the clinical status of a patient if the dose is such that the eosinophil count does not drop. On the other hand, the eosinophil is such a sensitive indicator that the eosinophil count can drop to substantially zero in the peripheral blood with no change in the clinical status of the patient in some cases. The eosinophil count remains low

throughout the period of maximal adrenal cortical stimulation although it may rise to the pre-treatment base line or over as the dose is decreased to maintenance levels.

b) Lymphocytes

The lymphocyte count in the peripheral blood is a less sensitive indicator of adrenal cortical stimulation than the eosinophiles, in that the count of the peripheral blood seldom drops more than 50 per cent. The lymphocyte count differs further in the fact that the count, under continued ACTH administration, is inclined to return to pre-treatment base line levels.

c) Polymorphonuclear Cells

Although there is a considerable individual variation in the sensitivity of the polymorphonuclear cell count to adrenal cortical stimulation, there is a distinct tendency for the polymorphonuclear count to rise 50 to 100 per cent above the base line level under ACTH administration. In some cases the count remains high throughout the period of stimulation, whereas in others it may return to the pre-treatment base line.

d) Red Blood Count

In the person with an anemia associated with diseases affected by ACTH, there is likely to be a reticulocytosis and a trend for the red cell count to return to normal on continued administration of ACTH. This, of course, may be a reflection of a reversal of the disease process in the case in question. There is no apparent effect on the red blood cell count when this is normal during the pre-treatment period.

e) Platelets

The platelet count is inclined to rise on ACTH administration and this may be marked in thrombocytopenic purpura or other situations where the platelet count is low.

2. Blood Changes

a) Sedimentation rate and plasma fibrinogen.

In diseases associated with a high red blood cell sedimentation rate and a high plasma fibrinogen, there is a return of both of these to normal levels in cases of disease reversed by ACTH administration.

b) Gamma Globulin

In diseases, such as lupus erythematosis, which may be associated with a high gamma globulin in the serum, there is a trend for this to return to normal levels under ACTH administration concurrently with clinical improvement, although the clinical improvement may precede the return of the gamma globulin concentration to normal levels by several weeks.

c) Albumin

In diseases such as nephrosis and states of malnutrition where the serum albumin may be below normal, there is a tendency for the serum albumin to return to normal levels on continued ACTH administration and as the patient improves.

3. Kidney Function

There is definite evidence that the renal threshold is decreased when the adrenal gland is stimulated with ACTH, and this may result in glycosuria without hyperglycemia, as noted above.

Likewise, there is a greater clearance of uric acid in the blood immediately following ACTH administration, and particularly in cases of gouty arthritis in which this may be the major factor in aborting the gout attack.

Recent experiments suggest that there is no marked increase in uric acid production on ACTH stimulation except in lymphomatous tumors and the such, where tremendous quantities of cells are being resolved.

4. Enzymes

Adrenal cortical stimulation may alter a number of enzyme systems among which may be mentioned the following:

a) Lysozyme

It has been a well-established fact that the lysozyme excretion in the intestine of ulcerative colitis cases is high and it has been hypothesized that the depolymerizing action of this enzyme on mucus may be the cause of this syndrome. The effect of ACTH on this disease may be the marked decrease in the secretion of this enzyme under adrenal cortical stimulation.

There are a number of other enzyme systems that have been studied, but their role in disease states is not sufficiently clear to draw any correct correlation.

In general, it may be said that every enzyme system and every enzyme inhibitor system studied to date is altered when ACTH is administered. This reflects the fact that the major action of the adrenal corticoids may be at the tissue cell level.

FUNDAMENTAL AND BROAD PHYSIOLOGIC PHENOMENA OBSERVED ON ADRENAL CORTICAL STIMULATION.

Quite apart from all of the above phenomena, there are certain basic phenomena that should be considered that may be related at the very fundamental level to the occurrence of a number of disease states and their reaction to ACTH administration.

1. ACTH appears to render cells immune to a wide variety of known toxic agents. Examples are:

   a) Bacteria

   A patient may have a pneumococcal septicemia without fever, or without any clinical evidence of such an infection and, likewise, the pneumonia in the case in question may resolve rapidly with immediate associated development of a sense of well-being.

   b) Antigens

   Individuals known to be highly sensitive to specific antigens or drugs can be exposed to these antigens or drugs while under ACTH administration with no deleterious effect whatever. Likewise, the clinical syndromes associated with hypersensitivity phenomena can be blocked completely in patients already exposed.

   c) Chemicals

   A patient sensitive to chemicals such as iodine, aminopterin, or mustard gas can have these chemicals administered while on ACTH administration, with no deleterious effects.

All of the above would appear to reflect a change in the tissue cells to the end that they do not react to known toxic agents. This may reflect a decrease in the cell permeability but the facts are that no one knows for sure.

2. Inhibition of Inflammatory Reaction

The administration of ACTH inhibits acute inflammatory reactions from almost any cause, thus acute inflammatory disease of the eye clears up at a remarkable speed; likewise, almost all other acute inflam-

matory processes, almost regardless of cause, are inhibited or blocked by adrenal cortical stimulation.

3. Inhibition of Excessive or Prolonged Fibroblastic Proliferation.

ACTH administration inhibits or blocks excess fibroblastic proliferation almost regardless of cause, and this may well be one of the basic mechanisms involved in a number of chronic proliferative diseases, such as rheumatoid arthritis.

4. Inhibition of Fever.

The administration of ACTH to patients with fever from almost any cause results in a return of the temperature to normal. Here, again, is a fundamental phenomenon that spreads over a wide area of disease and it is of course possible that this alteration towards normal may play a part in the reversal of the disease syndrome in question.

5. Inhibition of Pain.

Another fundamental aspect of adrenal cortical stimulation is the fact that pain from almost any cause may be diminished or blocked by the administration of ACTH, and whatever is behind this fundamental phenomena may have some bearing on the ability to reverse disease processes.

6. Adrenal Cortical Stimulation and Central Nervous System Physiology.

Most patients receiving ACTH are inclined to develop a sense of well-being and a sense of mental activity bordering on euphoria, regardless of the disease in question. Electroencephalographic recordings of patients on ACTH administration reveal that the alpha waves are of both larger magnitude and shorter intervals, which suggests that there is an effect upon the physiology of the individual neurones.

On the other hand, the patient on high doses of ACTH should be watched carefully from a psychiatric viewpoint since overstimulation may bring subclinical psychoses to the clinical level in some cases.

SUMMARY

1. In summary, the adrenal gland controls a number of the important metabolic and physiologic processes in the body.

2. There appears to be no direct correlation between the metabolic processes altered by adrenal cortical stimulation and disease processes or their reversal.

3. The correlation between adrenal cortical stimulation and disease processes and their reversal is more likely to be in the area of physiological effects at the tissue cell level, since these are altered appreciably and concurrently with clinical improvement of the patient under ACTH administration on doses that may cause no detectable metabolic shifts.

GENERAL PRINCIPLES TO BE CONSIDERED IN USING ACTH

1. VARIATION IN ADRENAL GLAND SENSITIVITY TO STIMULATION BY ACTH

It is important to realize that the adrenal glands of different individuals vary considerably in their sensitivity to stimulation by ACTH, and in consequence there is no specific, constant, uniform dose that is effective in all individuals.

A few individuals have glands that are extremely sensitive to ACTH stimulation. In such individuals doses of as little as 5 mgm. of ACTH four times a day have been sufficient not only to cause a complete remission of the disease in question, but also to cause definite metabolic shifts of the gland along the lines outlined above.

On the other hand a few individuals require doses as large as 50 mgm. of ACTH four times a day, and even at this level the clinical effect may be slight and the metabolic effect non-detectable. Fortunately, this type case is not common.

In general 25 mgm. of ACTH four times a day is sufficient to cause definite metabolic alterations in the body of most individuals, and this dose level should be avoided except where the clinical effect cannot be obtained at lower doses or when there is a definite intent to study metabolic alterations.

On the other hand 12.5 mgm. of ACTH four times a day causes relatively slight or even non-detectable metabolic alterations in most individuals, and is therapeutically effective in a substantial number of cases suffering from a variety of disease syndromes.

2. DOSAGE RANGE OF ACTH

In view of the fact that metabolic alterations are to be avoided if possible, as a general principle, it is desirable to start a case on a dosage level that will not cause a metabolic shift in most individuals. In consequence, in most diseases, it is desirable to start the patient on a 10 to 12.5 mgm. of ACTH four times a day and to hold the patient on this dose level for several days to ascertain if a clinical effect can be obtained before increasing the dose.

If no clinical effect is noted for 72 to 96 hours, the dose may be increased to 15 mgm. of ACTH four times a day.

If no detectable clinical effect is obtained after 48 to 72 hours at this dose, the dose should be increased to 20 mgm. four times a day.

Finally, if no clinical effect is noted after 48 to 72 hours on 20 mgm.,the dose is to be increased to 25 mgm. four times a day or more if necessary.

In working at these higher dosage levels, however, it should be kept in mind that metabolic alterations are likely to occur and doses above 25 mgm. four times a day should not be used without a full realization of the altered metabolic processes that may be in progress.

Another general principle to be kept in mind with regard to dosage range is that infants and young children require a larger dose per kilo of body weight than do older children and adults.

3. INTERVAL BETWEEN DOSES OF ACTH

Considerable evidence has accumulated that indicates that ACTH is rapidly destroyed in the body and likewise that the adrenal cortical hormones resulting from ACTH stimulation are metabolized rapidly. Accumulated evidence also suggests that the clinical and physiological effect of a given dose of ACTH is largely worn off in approximately 6 hours. In consequence, if a maximal clinical effect on a minimal daily dose is desired,the daily dose should be divided into four injections 6 hours apart.

Some investigators have found that they can get satisfactory results by dividing the total daily dose of ACTH into three injections 8 hours apart, but it is our general impression that it will require a larger total daily dose on an 8 hour dosage schedule than will be required if the total daily dose is divided into four parts and injected 6 hours apart.

Most investigators have found that the division of the total daily dose into two injections 12 hours apart has resulted in only slight or a very slow reversal of the disease process in question even when very large total daily dosages of ACTH have been administered.

Finally, the injection of the total daily dose of ACTH in a single injection has resulted in no appreciable change in the clinical status of most patients even when as much as 200 mgm. per injection is administered in a single daily dose.

4. DETERMINATION OF MINIMAL EFFECTIVE MAINTENANCE DOSE OF ACTH

As a general principle the total daily dose of ACTH in any given disease syndrome should be decreased as rapidly as possible consistent with maintaining a remission of the disease in question.

The 6 hour dosage schedule should be maintained until each individual injection is of the order of 5 to 10 mgm. per injection. The next daily dosage decrease may be accomplished by giving the same size individual dose that was used on the 6 hour dosage interval at an 8 hour dosage interval.

Finally, if the patient is maintained on an 8 hour dosage interval, an attempt may be made to maintain the patient on the same dose at a 12 hour interval. Some cases with some diseases cannot be maintained on a 12 hour interval, and it may be desirable to go back to the 8 hour dosage schedule and try to maintain the remission on a lesser quantity per injection since this has been possible in a number of cases.

If the patient can be maintained on a 12 hour dosage schedule, an attempt should be made to cut the dose further to a single injection every 24 hours. This has been successful in some cases.

In ascertaining the minimal effective dose there is a general principle that in most chronic diseases it is desirable to hold the patient on a given dose and dose schedule for at least a few days to ascertain the effectiveness of the dose and dose schedule being evaluated, before further decreasing the dose.

5. MAINTENANCE DOSAGE OF ACTH

As a general principle it is desirable to ascertain carefully the minimal maintenance dose of a given case of any chronic disease such as rheumatoid arthritis and to keep the patient on this minimal maintenance dose as long as possible. Some cases of such chronic diseases, who have been under study for a considerable period of time, have reached the point that a single small (10 mgm.) dose of ACTH per day, or even every few days,have been in substantial clinical remission. It is, of course, theoretically possible that many cases may be eventually taken off ACTH without a return of the disease in question, although long continued therapy may be required in many cases before this is accomplished.

6. TYPE CASE AND RESULTS TO BE EXPECTED ON ADMINISTERING ACTH

As a general principle cases treated shortly after the onset of a disease in question are more likely to be gotten into a remission more completely, quicker and on a smaller dose than is likely in long standing active cases of the same disease.

Likewise, as a general principle, cases treated shortly after the onset of a disease in question are more likely to remain in remission on tapering and more likely to remain in remission on stopping ACTH administration than long standing active cases of the same disease.

7. TAPERING THE DOSE OF ACTH

In the case of all patients treated with ACTH the administration of the hormone should not be stopped suddenly at a high level dosage administration except through a necessity because there is definite evidence that there is a period of adrenal cortical hypofunction for

for two to five days after cessation of administration of the hormone. As a general principle the dose should always be tapered as outlined above under "Determination of Minimal Effective Maintenance Dose" in order to allow the patient's own pituitary to take over the secretion of endogenous ACTH for his own adrenal cortical stimulation.

8. GENERAL PRECAUTIONS

(a) Sodium Chloride Intake

In view of the electrolyte effect of adrenal cortical stimulation which was discussed earlier, it is a good general principle to keep the sodium chloride intake at a minimal practical level, particularly when larger doses of ACTH are being employed, in order to minimize sodium and chloride retention with concurrent fluid retention and resulting edema.

Sodium Chloride and fluid retention with resulting edema is seldom a problem at the lower dosage levels, and as noted above, even on higher dosage schedules the retention may be only temporary.

If fluid and electrolyte retention continues and edema or other physiologic evidence of retention occurs, it should be kept in mind that practically all patients not having permanent kidney damage diurese the retained fluids and electrolytes on stopping ACTH. Consequently, if edema or retention presents a problem, it should be kept in mind that it may be desirable to omit injections of ACTH until diuresis occurs. Alternatively a diuretic may be given the patient to accomplish diuresis.

In most syndromes the omission of the dosage required to allow diuresis does not substantially alter the reversal of the disease process.

(b) Potassium Intake

In view of the fact that there may be a substantial urinary excretion of potassium on adrenal cortical stimulation by ACTH as noted in the earlier discussion, it is desirable to put the patient on a high potassium intake to avoid the risk of potassium deficiency, and this is particularly true when using the larger dosage schedules. Many investigators use the acetate salt in substitution for this sodium and administer 1/2 to 1 gram daily in the lower dosage schedule and 2 to 5 grams daily at the high dosage schedules. If the facilities are available, the blood potassium should be checked once or twice a week, particularly on the higher dose schedules. Likewise, electrocardiograms should be taken two or three times a week on high dose patients' cases, and once or twice a week on patients on lower doses of ACTH to detect potassium deficiency.

If the patient complains of fatigue or muscular weakness the potassium situation should be reviewed since this may be evidence of potassium deficiency.

(c) Fluid Intake and Output

It is desirable in the early stages of administration to keep an accurate record of the fluid intake and output since this will be

helpful in evaluating any weight gain that may occur and to ascertain whether the weight gain represents the retained fluid or actual gained weight.

Likewise, it may be well to restrict the fluid intake moderately, particularly when higher dosage schedules are being used.

(d) Diet

As noted in the discussion of the metabolic effects of adrenal cortical stimulation, there may be increased excretion of nitrogen, particularly at the higher ACTH dosage schedules, and it may be desirable to put the patient on a high protein diet during the study period. This is usually not important in the lower dosage ranges. Likewise, the diet must be considered in the light of the increase in appetite that occurs in so many patients to whom ACTH is administered.

9. LABORATORY CRITERIA OF ADRENAL CORTICAL STIMULATION

(a) Eosinophils

The most sensitive objective index of adrenal cortical stimulation, as noted earlier, is the eosinophil count in the peripheral blood and several pre-treatment base line eosinophil counts should be done daily for one or more days before undertaking a study of a given patient. The eosinophil count should be done by the direct counting chamber method of either Randolph (1) or Thorn.(2) Both are equally accurate in competent and conscientious hands, but most investigators believe that Randolph's method allows more uniform counts in routine laboratories.

The average of the eosinophil count in the normal adult or child is of the order of 200 cells per cubic millimeter. The eosinophil count should then be done 4 hours after the first morning injection for the first 3 or 4 days of study to ascertain the decrease in the eosinophil count after adrenal cortical stimulation. The decrease in the eosinophil count after ACTH administration is usually 50% or more under the pre-treatment base line level.

Once an adequate fall in the eosinophils is obtained, eosinophil counts daily or every few days during ACTH administration will serve as a useful guide of the state of adrenal cortical activity.

In general, the eosinophil count is only a "rough and ready" index of adrenal cortical stimulation and the eosinophil count may decrease substantially without attaining a remission in a given case, which reflects the sensitivity of this objective observation, and a disappearance of the eosinophils from the peripheral blood does not necessarily mean that the adrenal gland is being stimulated adequately to bring a given disease process under control.

Occasionally, an extremely high initial eosinophil level when on an allergic basis will not decrease promptly or markedly, although

adequate adrenal cortical stimulation is being obtained as reflected by clinical improvement.

On the other hand, a marked decrease or disappearance of the eosinophils from the peripheral blood in most individuals is associated with clinical improvement in a wide variety of disease syndromes. If the eosinophil count is high or in the order of a good many hundreds or even several thousands in the peripheral blood, it may require a very substantial dose to get them even down to the normal level in the peripheral blood, and in this situation a decrease of 100% or more in the count between the pre-treatment period and the treatment period is, in most cases, associated with clinical improvement or reversal of the disease process.

On the other hand, if the eosinophil count is below normal during the pre-experimental control period it may be an indication that the patient's adrenal gland is already under stimulation by the patient's own endogenous ACTH and, in this situation, it sometimes takes a substantial dose to cause a marked decrease or a disappearance of the eosinophils from the peripheral blood, and some individuals in this situation have, in fact, had a reversal of the disease process without a marked change in the eosinophil count as compared between the pre-experimental period and the study period.

In rare instances where an initially low eosinophil count exists, it may not be due to already active stimulation of the patient's adrenal gland, but due to a decreased production of eosinophils. The eosinophil count under such circumstances is not a useful measure of adequate adrenal cortical stimulation.

(b) Uric Acid-Creatinine Ratio

An increase in the uric acid-creatinine ratio as compared between the pre-treatment period and the treatment period has been reported by Thorn to be evidence of adrenal cortical stimulation, and it may be desirable to do this determination in the pre-experimental period and 4 hours after the first injection as outlined by Thorn, et al (2). This finding is not entirely uniform and constant in different individuals and, in consequence, is not of substantial value in studying disease syndromes.

(c) Urinary Excretion of 17 Ketosteroids

Most investigators are in agreement that increased urinary excretion of 17-ketosteroids is the most direct and constant evidence of adrenal cortical stimulation in the human being, and where these facilities are available this determination should be done. It is not of any practical value in assessing adequate dosage in undertaking the study of a case because of the long time required to get the results back.

On the other hand, it is a good record of the degree of adrenal cortical stimulation that occurs during an experimental study.

10. GENERAL CLINICAL CRITERIA OF ADRENAL CORTICAL STIMULATION

There are several symptoms and signs in various disease syndromes that may be a clue to adequate adrenal cortical stimulation by ACTH, which may be noted as follows:

(a) Temperature

In disease syndromes associated with the temperature, the temperature returns to normal in a period of 6 to 18 hours in almost all cases on adequate dosage of ACTH, more or less regardless of the cause of the temperature, and in the light of experience this decrease in temperature is, in most cases, associated with clinical improvement occurring either at the time or beginning some hours or even several days thereafter.

Likewise, in syndromes associated with a temperature, the rise in the temperature on decreasing a given dosage schedule is an indication of escape or inadequate stimulation of adrenal cortex by ACTH to get the disease syndrome under control.

On the other hand, if a patient develops temperature while on a given dosage schedule and particularly if the patient is on a relatively high dosage schedule, 100 mgm. to 150 mgm. a day, further administration of ACTH should be stopped for a number of hours in order to evaluate the cause of the temperature. This is important because many symptoms and signs of a number of different acute situations may be masked by maximal adrenal cortical stimulation.

(b) Pain

Disappearance of pain in any given syndrome is likewise an early index of beginning reversal of a given disease process, and if the pain begins to decrease on a given dosage schedule the patient should be held at that dosage for several days to ascertain the degree and rate of remission that is likely to occur.

Likewise, a reappearance of pain in joints or sites where pain was present prior to the study is a good index in guiding the degree and rate at which the daily dosage schedule can be decreased.

On the other hand, if pain not associated with the lesions under study, and particularly abdominal pain should occur during the study period, the administration of ACTH should be stopped until an evaluation of the cause of the pain may be accomplished. This is again necessary as in the case of temperature, since symptoms and signs of a number of acute situations may be thoroughly masked, particularly when the patient is on a high dosage schedule.

11. CONTRAINDICATIONS

(a) Hypertension

Since adrenal cortical stimulation with ACTH may cause electrolyte and fluid retention, particularly with high dosages, the use of this hormone in the presence of known hypertension should be avoided, and if a study is undertaken in such a patient despite this contraindication, adequate studies should be undertaken to make sure that the hypertension is not aggravated.

(b) Diabetes Mellitus

Since ACTH has a profound effect on carbohydrate metabolism, patients with other diseases who concomitantly have diabetes should not be treated until the physiologic inter-relationship of the adrenal cortex and the pancreas is further clarified.

On the other hand, the evidence to date appears to indicate that mild diabetics can be studied at the lower dosage levels of ACTH with no appreciable alteration in the diabetic state.

It may be said that in all of the cases thus far studied at high dosage levels where glycosuria or hyperglycemia developed during the study period, the glycosuria and hyperglycemia disappeared at the end of the experimental study.

(c) Chronic Nephritis

In view of the electrolyte and fluid retention that may occur on adrenal cortical stimulation, patients with chronic nephritis concomitantly with the disease under investigation should, in our opinion, be omitted from the study since they may not, in fact, be able to diurese the fluid and electrolytes retained.

(d) Known Psychotics and Psychopathic Personalities

In view of the fact that there is a substantial alteration in cerebral function in patients under study with ACTH, and in view of the fact that the role of the adrenal gland in mental disease is so far from clear, psychotic patients or patients with psychopathic personalities concomitant with diseases under study should not be treated with ACTH.

(e) Cushing's Syndrome

Since this syndrome results from excessive adrenal cortical function ACTH is not indicated in this disease.

(f) Congestive Heart Failure

In view of the fact that ACTH administration may cause electrolyte and fluid retention, it should not be used in the presence of congestive heart failure unless there is reason to believe that cardiac function will increase on ACTH administration as may occur in acute rheumatic fever and careful studies should be done in this case.

(g) Hirsutism

Cases of hirsutism should not be treated with ACTH because the occurrence of this syndrome may be evidence of excess adrenal androgen production and this may be exaggerated by ACTH administration.

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DIRECTIONS FOR USE OF ACTH IN SPECIFIC DISEASE SYNDROMES

In approaching the problem of treating specific disease syndromes with ACTH, it should be re-emphasized that the desirable goal is to obtain a therapeutic effect with minimum metabolic alterations.

For convenience, disease syndromes may be broken down into the following groups:

1. Endocrine dysfunctions
2. Metabolic diseases
3. Collagen diseases
4. Hypersensitivities
5. Acute inflammatory diseases of the eye
6. Acute inflammatory diseases of the skin
7. Acute inflammatory diseases of intestinal mucosa
8. Nephrotic syndrome
9. Blood diseases
10. Neuromuscular dysfunctions
11. Mental disease
12. Miscellaneous
13. Contraindications

1. ENDOCRINE DYSFUNCTIONS

The first published use of ACTH was reported by Dr. George Thorn and his associates (1) as a test for the functional reserve of the adrenal cortex.

A. The Thorn Test.

This consists of a single intramuscular injection of 25 mg. of ACTH with a comparison of the change in the circulating eosinophil count and uric acid/creatinine urinary excretion ratio before and after the injection.

Procedure for the test: No food is given after 8 P.M. and water should be likewise restricted after 8 P.M. on the day preceding the test. On the day of the test, 200 cc. of water is given at 6 A.M., 8 A.M., and 10 A.M. Urine is collected from 6 A.M. to 8 A.M. At 8 A.M. an eosinophil count is made either by the method of Thorn et al (1) or Randolph (2). The Randolph method

is recommended as the method of choice in routine laboratories.* Immediately thereafter, 25 mg. of ACTH is injected intramuscularly. Urine is collected from 9 A.M. to 12 noon. Another eosinophil count is made at 12 noon. The two specimens of urine are analyzed for uric acid and creatinine content.

The absolute decrease in circulating eosinophils at the noon count is expressed as the percentage fall from the initial count (normal range + 200). The percentage change in uric acid/creatinine ratio between the 8 A.M. specimen and the noon specimen is computed.

Interpretation of the test: A percentage fall in eosinophils of fifty per cent or more below the preinjection level, and an increase of fifty per cent or more in the uric acid/creatinine ratio over the preinjection ratio usually indicates a satisfactory adrenal cortical response. Such changes in all probability eliminate the possibility of adrenal cortical insufficiency.

B. Applications of the Thorn Test.

(1) As a test for the diagnosis of suspected adrenal cortical insufficiency, or Addison's disease. If the above changes do not occur, the adrenal cortical function may be considered to be impaired. The magnitude of the change is roughly proportional to the amount of adrenal cortical reserve. Thus, a fully adequate adrenal cortical reserve is frequently shown by a complete disappearance of the circulating eosinophils 4 hours after the intramuscular injection of 25 mg. of ACTH.

* The counting chamber differentiation of eosinophils with glycol stain diluting fluid

Stock Solutions

0.1 per cent Methylene Blue in Propylene Glycol	0.1 per cent Phloxine in Propylene Glycol

Working Solutions

Dilute above stock solution with an equal amount of distilled water	Dilute above stock solution with an equal amount of distilled water

Final Stain

Mix an equal number of drops of the two working solutions prior to use as white blood cell diluting fluid.

(2) As a test of the adrenal reserve pre- and postoperatively, as described by Thorn and his associates (3).

In major surgery, the adrenal hormones of the "11-17-oxy" type are of vital importance in the reaction of the organism against stress. Hence, the importance of any clinical indicator revealing the presence of these hormones in adequate amounts. Major surgery, itself, places sufficient stress on the body to cause increased secretion of 11-17-oxysteroids by the adrenal cortex. This increased secretion of hormones may be measured by a fall in the circulating eosinophil count. Therefore, the Thorn test may be used preoperatively to determine whether or not the patient has an adequate adrenal cortical reserve to meet the stress of major surgery successfully. The following points have been determined clinically:

(a) In the presence of normal adrenal cortical activity there is an almost complete disappearance of circulating eosinophils during the first 24 to 48 hours after a major operation.

(b) There is usually a sharp rise of the eosinophil levels on the second and fourth postoperative day, associated with clinical improvement. This "third-day eosinophilia" is associated with return of normal adrenal cortical reserve.

(c) The finding of an eosinopenia during the first 24 to 48 hours after a major operation is, in itself, evidence of increased adrenal cortical activity.

(d) Conversely, the finding of a normal or high eosinophil level during the first 24 to 48 hours after an operation suggests adrenal cortical insufficiency, in the absence of allergy. The prognosis in this instance is poor, and therapy with either ACTH, if the adrenal is capable of responding to it, or with adrenal cortex extract is indicated.

(e) The measurement of eosinophil fall four hours after the injection of 25 mg. of ACTH before operation is a good index of the capacity of the adrenal cortex to secrete 11-oxysteroids and furnishes a good means of preoperative prognosis.

(f) A negative response to the Thorn test preoperatively indicates reduced adrenal function and suggests a guarded prognosis. If treatment is required either during or after operation, ACTH should be given if the adrenal is able to respond, or adrenal cortex extract if it is unable to respond.

(3) Differential diagnosis of panhypopituitarism or functional hypopituitarism.

The Thorn test is an excellent test to differentially diagnose panhypopituitarism or functional hypopituitarism and Addison's disease. In the first two syndromes the Thorn test may be positive, whereas in Addison's disease it will be negative. It should be kept in mind in undertaking the differential diagnosis of these syndromes that panhypopituitarism and functional hypopituitarism are often accompanied by hypothyroidism and if the basal metabolic rate is low the result of the Thorn test may be either negative or equivocal. In this situation it may be necessary to administer thyroid hormone to bring the BMR up to normal and repeat the Thorn test, which will then be positive in a number of cases in which it was negative in the first instance. Furthermore, in differentially diagnosing panhypopituitarism and functional hypopituitarism from Addison's disease it should be kept in mind that in long-standing cases of panhypopituitarism and functional hypopituitarism the Thorn test may be negative even though thyroid hormone is administered, because of the long-standing non-function and possible atrophy that may have occurred as a result of pituitary hypofunction. In these cases it may be desirable to administer ACTH (Armour) in 25 mg. doses every 6 hours for a period of 2 to 3 weeks, during which time full function of adrenal cortical reserve may reappear.

C. Treatment of Panhypopituitarism and Functional Hypopituitarism.

As noted above, long-standing cases of panhypopituitarism and functional hypopituitarism may be only slightly responsive to ACTH stimulation and, as noted above, large doses may be required for a number of days before adrenal cortical reserve returns to normal. In these diseases the BMR should be brought to normal by administration of thyroid extract before undertaking ACTH therapy.

Less long-standing cases may demonstrate a full adrenal cortical reserve if the basal metabolic rate is normal and 10 mg. of ACTH (Armour) or less every 6 hours may result in a full clinical effect.

In the case of long-standing cases it may be desirable to administer 25 mg. every 6 hours until adrenal cortical reserve approaches normal, after which the dose may be gradually decreased to one that will give a full clinical effect without metabolic evidence of adrenal cortical overstimulation. The dose for this purpose may range from 5 to 20 mg. every 6 hours, and some cases may be kept under full control on doses of this range once, twice, or sometimes three times daily.

2. METABOLIC DISEASES

A. Gout.

Wolfson et al (4) have reported that the following treatment regime will control most cases of acute gouty arthritis, and the following dosage schedule is recommended:

The basic principles are as follows: Colchicine and ACTH are begun simultaneously and given together at 6-hour intervals until 75% to 90% improvement is attained. ACTH is then discontinued, while colchicine is continued to prevent an attack due to ACTH withdrawal. Laboratory observations are made to determine, first, how responsive the patient's adrenal cortex is to ACTH when treatment is begun and, secondly, the correspondence between therapeutic results and a good adrenal response.

(1) Schedule for the initial dose of ACTH:

Hour 0: Patient is fasting. Discard urine.
Hour 1: Collect urine secreted since hour 0 for determination of basal uric acid/creatinine ratio. Draw blood for total leukocyte and eosinophil count. Give 50 mg. of ACTH i.m. and .00065 of Lilly colchicine by mouth.
Hour 4: Discard urine.
Hour 5: Collect urine secreted since hour 4 for determination of uric acid/creatinine ratio. Draw blood for total leukocyte and eosinophil count.
Hour 7: Evaluate patient's status. If patient has 75% to 90% improvement, i.e., if only Grade 1 subjective and objective symptoms remaining, proceed as in Section (3). Otherwise follow Section (2).

(2) Schedule for further doses of ACTH:

Hour 0: Give 50 mg. of ACTH i.m. and .00065 of Lilly colchicine.
Hour 3: Discard urine.
Hour 4: Collect urine secreted since hour 3 for determination of uric acid/creatinine ratio. Draw blood for total leukocyte and eosinophil count.
Hour 6: Evaluate patient's status, as described above.

(3) When 75% to 90% improvement has been attained:

Continue to give .00065 mg. of Lilly colchicine orally q.i.d. until patient develops beginning diarrhoea. Discontinue colchicine for 24 hours and treat diarrhoea, if necessary, with paregoric and bismuth preparations. After 24 hours

resume colchicine .00065 t.i.d. If diarrhoea again recurs, reduce this dosage to .00065 mg. b.i.d. When the maximum dose of colchicine tolerated daily without diarrhoea has been found, continue to give this ration for at least two weeks. It may be continued indefinitely, however, without danger and exerts a marked prophylactic effect against recurrences.

(4) Comments:

About 2 in every 4 patients will probably require only one dose of ACTH, 1 in 4 will require two doses, and 1 in 4 will require three or more doses. Administration of salicylates is not advised since these vitiate the value of determining the urine uric acid/creatinine ratio. Lilly colchicine has been stipulated because of its marked uniformity in potency which is not shared by the other commonly available preparations. Any recurrences which may be seen after ACTH is withdrawn should be particularly carefully noted and treated as if they represented new attacks. Such recurrences, however, are distinctly rare.

B. Idiopathic Hypoglycemia.

McQuarrie et al (5) have reported excellent results in the use of ACTH in spontaneous hypoglycemia in infants and children, and goes so far as to say that "ACTH may be as effective in the control of chronic non-Addisonian hypoglycemosis in many instances as insulin is in the control of pancreatic diabetes". The dosage may vary widely in this syndrome, depending on the severity of the case in question and the age of the patient, and the effective dosage must be determined in each case with the eosinophil count and the blood sugar level representing the clues to adequate dosage, with the greater emphasis being placed on the latter, the aim being to get the blood sugar level to normal, or above. McQuarrie found the dose to accomplish these ends between 3 to 10 mg. 4 times a day, at which levels he found the hypoglycemia to be overcome with the disappearance of the convulsions commonly associated with this syndrome. Particularly interesting is the fact that he found that the single administration of 10 to 20 mg. of ACTH in a single dose every 48 to 72 hours adequate to control the hypoglycemic state after an intensive therapeutic regime of approximately 10 days' duration.

3. COLLAGEN DISEASES

As in most other diseases, there is a wide variation in the therapeutically effective dose in different individuals with one or another of the collagen diseases and this must be kept in mind in undertaking the treatment of any given case. Again it should be emphasized that early, acute cases of the collagen disease group do better, in general, on a lower dose than is the case in long-standing severe disease.

A. Rheumatoid Arthritis.

The therapeutically effective dose of ACTH (Armour) in rheumatoid arthritis varies widely but, as a general principle, it is better to start the patient on 10 to 12 mg. of ACTH q.6.h. and keep the patient on this dose for several days to ascertain if a therapeutic effect is being obtained. If no effect is noted after several days, the dose should be increased to 15 mg. q.6.h. and finally, if no improvement is noted after several days on this schedule, the dose should be increased to 20 mg. q.6.h., if necessary. Most patients respond to one of the above dosage schedules.

As noted previously, the minimal effective therapeutic dose should be explored after a full clinical and laboratory remission is obtained, which usually occurs in 7 to 21 days on adequate dosage. An attempt should then be made to ascertain what is the lowest effective dose and the longest dosage interval that can be obtained for the patient in question. This was outlined in the previous section under Determination of Minimal Effective Maintenance Dose (page 28).

It should be emphasized that maximum results cannot be expected in long-standing, severely crippled cases with deformity and contractures.

B. Acute Rheumatic Fever.

The results to date in the use of ACTH in acute rheumatic fever are among the most optimistic in the collagen disease group in that relatively small doses over relatively short periods of time have caused a reversal of the clinical disease in most cases and have blocked the severe heart disease that is usually associated with severe attacks of acute rheumatic fever. By far the best results have been in acute first or second attacks of rheumatic fever in individuals with no evidence of previous heart damage.

Thorn et al (6) reported the accomplishment of a rapid and complete clinical and laboratory remission of acute rheumatic

fever of short duration in children in a dose of the order of 10 mg. every 6 hours for 10 days to several weeks.

Massell et al (7) reported excellent results in 10 cases of acute rheumatic fever treated with 2-1/2 to 10 mg. of ACTH every 6 hours over a period of 10 days to several weeks, with gradually decreasing doses after the sedimentation rate and EKG returned to normal. In practically all of the acute, short-duration cases without previous evidence of heart damage, the attack was reversed without evidence of residual heart damage to date.

It should be emphasized that the use of ACTH in the presence of congestive heart failure should be undertaken with caution, since the retention of electrolytes and fluid may further increase the cardiac load and due precaution should be undertaken to assess the degree to which this may occur. In many cases this does not present a serious problem since the heart rate is inclined to decrease and the cardiac output increase with the result that the patient may come out of congestive failure while on ACTH. If such does not occur and the cardiac load becomes embarrassing, it may be desirable to stop the ACTH for several doses to allow diuresis to occur or, alternatively, to give the patient a diuretic.

The results in chronic active rheumatic fever and in cases with evidence of real or severe cardiac damage from previous attacks are not as optimistic as in the acute, short-duration cases without previous cardiac damage. In the case of active, long-standing disease, the management of the electrolyte and fluid retention problem is more difficult, because of the chronically damaged heart, and larger doses of ACTH are likely to be required in such cases. In all chronically active cases thus far studied, as in most cases of rheumatoid arthritis, the disease process becomes reactivated when the hormone is stopped and management of fluid retention in such cases renders maintenance therapy difficult. We do not recommend ACTH for the treatment of such cases at this time.

We recommend the use of ACTH primarily in cases of acute rheumatic fever in first or second attacks without evidence of severe pre-existing cardiac damage. The recommended dose is 5 to 7-1/2 mg. of ACTH every 6 hours in younger children and 10 to 12-1/2 mg. every 6 hours in older children. The clinical result should be evaluated for several days before increasing the dose.

When the effective dose is ascertained the patient should be kept on this dose until clinical and laboratory evidence of active infection has disappeared and then the dose should be gradually

decreased over the period of a week to 10 days on a 6-hour dose schedule until the level of 2.5 mg. of ACTH is reached, and then the hormone administration stopped. There may be a slight exacerbation of the disease for a period of days to a week or more subsequent to cessation of the hormone administration, but in most instances this subsides in a relatively short period of time. If this does not occur it may be well to reinstitute therapy and carry it on for a longer period of time at the minimal effective dose level and again taper the dose as above.

C. Lupus Erythematosis.

Lupus erythematosis presents a difficult problem, although the results of ACTH (Armour) administration may be both pronounced and rapid. The real problem in this syndrome is that this disease appears to require a larger dose for a clinical and laboratory therapeutic effect than most diseases. However, this may be because the majority of cases treated to date have been either very severely ill or even terminal before ACTH administration has been initiated and it may well be that earlier, less severe cases can be gotten into remission on a smaller dose in a shorter period of time.

In view of the fact that the standard beginning dose in this disease syndrome used by most investigators, Elkinton (8), Browne (9), Clark (10), and Howard (11), has been 25 mg. ACTH (Armour) every 6 hours, we would recommend that lower dosage schedules be explored, particularly in the earlier and less severe type cases in order to minimize the metabolic shifts that may occur at the higher dosage levels.

We recommend that where the condition of the patient will allow, the beginning dose should be 12.5 mg. ACTH (Armour) every 6 hours, and this dose should be maintained for 3 or 4 days to ascertain if a clinical effect can be obtained. In this disease, temperature may be a good clinical guide to effective dosage, and if the temperature does not return to normal after several days the dose should be increased to 15 mg. every 6 hours and increased further at 48-hour intervals to 20 and, if necessary, 25 mg. every 6 hours until the temperature returns to normal or other clinical evidence of improvement occurs.

Some of the severe and terminal or nearly terminal cases treated have required as much as 25 mg. every 4 hours or 50 mg. every 6 hours to control the temperature but these dosage ranges should be avoided unless adequate facilities are available to assess the degree of metabolic shifts that occur. Most of the patients treated to date have been maintained on the clinically

adequate effective dose for a period of 3 to 4 weeks, after which an attempt is made to decrease and taper the dose to ascertain if a clinical and laboratory remission can be attained without further administration of ACTH. To date approximately half of the cases treated have remained in remission after such a therapeutic course for a period of weeks to many months without further ACTH administration. Cases in this group have, by and large, been earlier, less duration cases than the other half who appear to require a maintenance dose to maintain a clinical and laboratory remission. This maintenance dose should be ascertained in the manner outlined under the general instructions in the use of ACTH.

The experience to date suggests that the minimal effective maintenance dose in lupus erythematosis disseminatus is something of the order of 20 to 45 mg. a day, divided into 2 or 3 doses. It is interesting that a minimal effective dose in the chronically treated patients to date has gradually decreased over the period of months, but it is only conjecture whether or not these patients will be able to be taken off ACTH entirely at some future date.

D. Dermatomyositis.

Since this is a relatively rare disease syndrome, not many cases have been studied to date, and minimal effective therapeutic and minimal effective maintenance dosages have not been determined. Most of the cases treated to date, Ragan, Milhorat (13), Schwachman (14), all used large doses of ACTH - 10 to 20 mg. q.6.h. in children and 25 mg. q.6.h. in adults - with marked clinical improvement. The two children have remained in clinical remission for some months, whereas most of the adults relapsed when ACTH administration was stopped.

No chronic administration minimal maintenance dose studies have been done to date. If a study of therapeutic effects of ACTH in dermatomyositis is to be undertaken, we recommend a beginning dose of 10 to 12.5 mg. of ACTH (Armour) every 6 hours for a period of several days, and that the dose be not increased unless there is no clinical effect and that the dose should be increased gradually until an effect is obtained, but not above 25 mg. q.6.h. without full consideration of the metabolic shifts that may occur. The patient should be maintained on the effective dose until full clinical and laboratory evidence of active disease have disappeared and after that, an attempt should be made to decrease and taper the dose along the lines outlined above, either to see if the patient can be gotten into a complete clinical remission without further ACTH administration, or to ascertain the minimal effective dose for the patient in question.

E. Periarteritis Nodosa.

This disease is so uncommon that few cases have been studied to date. Bassett et al (15) and Stillman (16) have each reported on the use of ACTH in one case of periarteritis nodosa using a dosage schedule of 10 mg. q.6.h. for a period of 14 and 12 days, respectively, during which they observed clinical and laboratory evidence of improvement. In both cases the disease relapsed when the hormone therapy was stopped.

Several other cases have since been studied and one very early case has remained in remission for a period of months. Several far advanced cases did not respond well to large doses of ACTH (25-50 mg. q.6.h.) and, on the other hand, two far advanced and severe cases have been reported to us in which there were widespread and extensive periarteritic lesions which healed under ACTH stimulation but unfortunately resulted in death from cardiac failure because of the resistance to circulation developed by the healing process in the peripheral vessels.

In the light of the above, we do not recommend ACTH in the treatment of periarteritis nodosa with the possible exception of very early, short-duration cases.

F. Scleroderma.

Bayles et al (17) have reported on the use of ACTH in four cases of scleroderma, all of which were severe and long-standing, in which they reported slight improvement on 10 mg. of ACTH (Armour) every 6 hours for a period of 12 days to 4 weeks.

We do not recommend the use of ACTH in this type of case since there is no evidence that adrenal cortical stimulation will cause an alteration of collagen already laid down. Theoretically, adrenal cortical stimulation with ACTH, if it has a place in scleroderma, would be in the early proliferative stage before appreciable collagen deposition has occurred, but by the nature of this disease it would appear that continued maintenance administration would be required for an indefinite period of time.

4. HYPERSENSITIVITIES

a) Bronchial Asthma

Randolph (18), Harvey and Howard (19), Rose (20), and others have reported on the use of ACTH (Armour) in chronic intractable asthma and status asthmaticus with excellent results in most cases.

Randolph reported a complete cessation of symptoms beginning a few hours after the first dose of 25 mg. of ACTH (Armour). He then continued the injection every six hours for a period of two to three days. He further reported that several of the cases remained free from asthma for a period of weeks and longer after cessation of administration of the hormone.

Harvey and Howard (19a) have used two different dosage schedules:

1. For moderate severe asthma they recommend 12.5 mg. of ACTH every six hours for a period of 10 to 14 days; afterwards the dose is tapered rapidly over several days. A majority of the patients studied on this dosage regime have remained in remission for a period of weeks to many months.

2. In very severe cases of status asthmaticus they recommend the following dosage schedule for ACTH (Armour):

   25 mg. every 6 hours for two to three days
   20 mg. every six hours for two days
   15 mg. every six hours for two days
    5 mg. every six hours for two days

   On this dosage schedule a majority of the patients have remained symptom free for a period of weeks to months, although some cases may relapse rapidly and appear to require a maintenance dose which must be determined for the case in question on an individual basis.

A few of these cases require short interval doses of ACTH, whereas others appear to do quite well on a single injection a day of the order of 10 to 20 mg. per injection.

Rose recommends the following dosage schedule:

25 mg. every six hours for three days
20 mg. every six hours for two days
a 25 mg. single injection the last day

with constantly good results.

In general, we recommend the smaller dosage schedule as outlined by Harvey and Howard above, except where the condition of the patient indicates that rapid relief is essential.

ACTH (Armour) has been used in a few asthmatic children, on a dose of 10 to 12.5 mg. q.6.h. However, on the basis of the results in adult asthmatics and the effect of ACTH in children in other diseases, it is likely that doses of 5 to 7.5 mg. q.6.h. may be adequate, except in extremely severe status cases.

b) Ragweed Hay Fever

The use of ACTH in hypersensitivity states was so late in being undertaken last year that relatively few cases have been studied, and these were reported by Randolph (21); and in view of the shortage of ACTH at the time, the cases studied were given large doses of ACTH (Armour) (25 mg. q.6.h.) for a period of 48 hours.

Three patients, severely sensitive to ragweed pollen, remained completely symptom-free for the rest of the ragweed hay fever season.

In view of the effect of ACTH in smaller doses in the other hypersensitivities, as well as the desirability of avoiding high doses of ACTH, we recommend the alternative treatment of 12.5 mg. of ACTH (Armour) every six hours for a period of ten days, as outlined under "Asthma" above.

c) Contact or Atopic Dermatitis

Few studies have been done in this syndrome and we do not recommend ACTH (Armour) for this purpose at this time. In view of the effect of ACTH in the other hypersensitivities, it is reasonable to forecast that the syndrome can be effectively blocked by adequate doses of ACTH and that the patient will remain free of symptoms thereafter if the known sensitizing agent can be identified and eliminated.

d) Drug Sensitivities

Harvey and Howard (22) et al have reported on the use of ACTH (Armour) in cases of severe penicillin sensitivity associated with fever, arthritis, giant urticaria and the such. They administered ACTH (Armour) on the following dosage schedule:

25 mg. every six hours for two days
20 mg. every six hours for one day
15 mg. every six hours for one day
10 mg. every six hours for one day
5 mg. every six hours for one day

There was striking improvement in all cases in six to eight hours and all skin discoloration had disappeared in thirty-six hours. There was no recurrence when the hormone was stopped.

They (23) have also reported on the use of ACTH in a case of exfoliative dermatitis precipitated by exposure to iodine in a patient known to be highly sensitive to iodine. There was a rapid disappearance of the exfoliative lesions and a return of the skin to normal over a period of days on a dosage of 25 mg. every six hours, and in this case the disease did not recur.

They have since observed (23) that other acute drug sensitivities can be blocked by the administration of ACTH. In general, they recommend the following:

25 mg. every six hours for two days

then rapidly tapering the dose as follows:

20 mg. every six hours for one day
15 mg. every six hours for one day
10 mg. every six hours for one day
5 mg. every six hours for one day

In some cases there may be a tendency to relapse, and in such situations the dosage should be increased to that previously effective, and held there for several days before again tapering the dose.

e) Giant Urticaria

ACTH has also been used in giant urticaria of unknown origin with effective results on a dosage schedule in most cases of 25 mg. every six hours for one day, during which the symptoms are likely to disappear; after which the dose has been decreased to 12.5 mg. every six hours and held at this level for several days, after which it may be tapered as above.

There appear to be some individuals in this category who require a minimal effective dose which must be determined in the individual case, where it is usually of the order of 10 mg. of ACTH (Armour) once, twice, and sometimes three times a day.

f) Loeffler's Syndrome

Rose (24) has reported on the use of ACTH (Armour) in Loeffler's syndrome, with dramatic results, on a dose of 35 mg. of ACTH (Armour) every 90 minutes, for a total of four doses. In one case a marked clearing of the pulmonary lesions occurred in a matter of hours, and this patient remained symptom-free for a period of many months.

Five other cases of Loeffler's syndrome have been treated by other investigators on a dosage level of 25 mg. every six hours until the chest plates were clear; which, in most cases, was 24 to 48 hours;

after which the dose was decreased to 12.5 mg. every six hours for three days, and then 5 mg. every six hours for several days. Two of the patients have remained symptom-free for many months, whereas three relapsed when ACTH (Armour) administration was stopped. It would thus appear that some cases of this syndrome may require continued minimal maintenance doses, which must be determined in each case.

g) Acquired Hemolytic Jaundice

Thorn et al (25), Diamond et al (26), Dameshek et al (27) and several other investigators have reported a rapid reversal of the blood picture to normal on administering ACTH (Armour) in cases of acquired hemolytic jaundice.

The standard dose used in most cases has been 25 mg. every six hours, and the patients have been held on this dosage for a period of several weeks until the blood picture returned to normal. Since this is a hypersensitivity disease, it is our belief that such large doses of ACTH (Armour) may not be required in most cases of acquired hemolytic jaundice, and we would recommend a dose schedule of 10 to 12.5 mg. every six hours for a number of days to ascertain if a clinical and laboratory effect are being obtained before increasing the dosage to higher levels. After the blood picture has returned completely to normal, an attempt should be made to taper the dose gradually over a period of a week or more along the lines outlined above. If 10 to 12.5 mg. of ACTH (Armour) every six hours is found to be effective, the dose should be held until all evidence of the disease has disappeared; the dose should then be decreased to 7.5 mg. every six hours for a period of several days, then to 5 mg. every six hours for several days before stopping the administration of the hormone.

Some cases have remained in remission for a period of weeks to months, whereas others relapse when the hormone is stopped or when the dose is cut below the minimal maintenance dose for the case in question.

In the case of cases appearing to require a minimal maintenance dose, theoretically, in the light of the results in the other hypersensitivities, it should be possible to wean these cases off ACTH at some stage, and this should be attempted periodically.

5. ACUTE INFLAMMATORY DISEASE OF THE EYE

Almost simultaneously Gordon and McLean (28), Olson, Smith et al (29) reported that ACTH had a marked effect on acute inflammatory diseases of the eye, among which may be listed the following:

Acute Iritis
Acute Keratitis
Acute Uveitis
Acute Chorioiditis
Optic Neuritis
Sympathetic Ophthalmia
Acute Secondary Glaucoma
Conjunctivitis

In line with the general principle that diseases which are treated shortly after the onset are easier to handle and are more likely to remain in remission after cessation of ACTH (Armour) administration, the results in acute inflammatory diseases of the eye to date indicate that a high majority of the cases that are treated shortly after the onset of the disease come into complete remission rapidly, and a high majority have remained in remission for a substantial period of time since the cessation of ACTH (Armour) therapy.

In contrast, long standing cases of the same diseases have required higher doses and longer periods of therapy to reverse the disease process and, furthermore, the majority of these relapse when the hormone is stopped or when the dose is cut below the minimal maintenance dose for the case in question.

Gordon and McLean used a dosage schedule of 25 mg. every six hours for a period of several days to approximately two weeks. On the other hand, Olson et al and Smith et al have used doses of 10 to 20 mg. every six hours with equally good results; and Thorpe and others have obtained equally good results in many cases on doses of 10 to 15 mg. of ACTH (Armour) every six hours, particularly in early cases.

In the light of experience, and on general principle, we recommend 10 to 12.5 mg. of ACTH (Armour) every six hours for a period of several days to ascertain if a clinical effect can be obtained before using higher doses; and if the latter appears to be indicated in the light of clinical effect, the dose should be increased to 15 mg. every six hours for 48 hours or more before going to higher dosage levels.

We also recommend that the patient be kept on the effective clinical dose until the eye lesion is healed and the dose should then be lowered gradually in the manner of treatment of some of the diseases discussed previously.

If the patient cannot be withdrawn from the hormone without relapsing, the minimal effective dose should be determined in each particular case. The ultimate aim is to ascertain the smallest dose that will keep a patient in remission for the longest interval between doses.

There appears to be no dosage differentiation between the different types of acute inflammatory diseases of the eye, although the effective doses may vary considerably in different individuals and, as mentioned above, long standing cases are likely to require larger doses for a longer period of time than are necessary in the early acute cases.

6. ACUTE INFLAMMATORY DISEASES OF THE SKIN

The acute inflammatory diseases of the skin that have been treated to date are:

a) Atopic and contact dermatitis of a hypersensitivity origin
b) Exfoliative dermatitis
c) Pemphigus
d) Psoriasis

a) Contact Dermatitis and Atopic Dermatitis

This has been discussed under the section of "Hypersensitivities" above.

b) Exfoliative Dermatitis

As noted earlier, the first case of acute inflammatory disease of the skin was treated by Harvey and Howard et al -- exfoliative dermatitis resulting from iodine sensitivity. Other cases of exfoliative dermatitis of both known and unknown etiology have been treated by other investigators.

The standard starting dose in this syndrome that has been used to date has been 25 mg. of ACTH (Armour) every six hours and in view of the extensive and serious nature of this disease it may be well to start a patient with this disease on this dosage schedule and hold the patient on this dose until definite evidence of improvement occurs. This may be as early as 48 to 72 hours, at which time an attempt should be made to decrease the dose to 20 mg. every six hours for several days. If clinical improvement is maintained, the dose should then be cut to 15 mg. every six hours, and finally to 10 mg. every six hours; and if clinical improvement is still maintained it may be desirable to hold the patient on this dose for approximately two weeks before further tapering the dose.

If the lesions reappear on a given decreased dose, the dose should be increased to the previously effective dose and held there for at least several days before again attempting to decrease the dose.

Some patients have remained in remission for substantial periods of time after the cessation of the hormone, whereas others, particularly those of unknown etiology and longer duration, appear to require a minimal maintenance dose which must be determined in each individual case along the lines outlined previously.

Here, again, it may be possible to eventually withdraw some patients at a later date who require maintenance doses in the beginning, and this should be explored from time to time in the case in question.

If the disease does not appear to be serious and overwhelming, it is, of course, desirable to ascertain if the patient can be put into remission on a lower dosage schedule; and in these cases we recommend a beginning dose of 10 to 12.5 mg. every six hours for several days to ascertain if clinical effect is being obtained before decreasing the dose. If a clinical effect is not obtained after several days on this dose schedule in these milder cases, the dose should be increased to 15 mg. every six hours for several days and, finally, 20 or 25 mg. every six hours if a clinical effect is not obtained.

In view of the wide individual variation of sensitivity to adrenal cortical stimulation, there may be some patients who require doses above 25 mg. every six hours, but these large dosage schedules should be undertaken with caution and with full realization of the metabolic alterations that may be in process.

c) Pemphigus

Harvey and Howard et al (30), Ragan et al (31), Thorn et al (32), and several other investigators have treated cases of pemphigus with ACTH (Armour) with at least temporary good results.

In view of the seriousness and extensiveness of this disease syndrome most investigators have used a standard starting dose of 25 mg. of ACTH (Armour) every six hours, and in cases where this is the clinically effective dose the new lesions have ceased to form in a period of 24 to 48 hours, and the old lesions resolve at a rapid rate over a period of a relatively few days. Most of the patients have been kept on the above dosage schedule for a period of several weeks or until all of the old lesions have healed; after which the dose has been discontinued.

Several of the cases have remained in clinical remission for many weeks to months after cessation of the hormone administration, whereas, on the other hand, some cases appear to require a minimal maintenance dose and one case has been on such a minimal maintenance dose for a period of over a year. It is interesting that the minimal maintenance dose in this case has been gradually decreased over the months to where 10 mg. two to three times daily allows a continuation of the remission - whereas in the beginning 25 mg. q.4.h. were required to stop the formation of new lesions, and in the beginning lesions began to reappear when the dose was cut to 25 mg. q.6.h.

As in all other maintenance dose situations, the minimal maintenance dose must be explored individually in each case in question, and the patient should be periodically re-explored to ascertain if the dose can be cut after being on a given dose for a reasonable period of time.

d) Psoriasis and Psoriatic Arthritis

Hench (33), Bauer (34), Holbrook (35), Markson (36), Wolfson (37), and others have studied the effect of ACTH in psoriasis and psoriatic arthritis. Some of the first cases studied were psoriatic arthritic cases, and in these cases the arthritis, except in very long standing, severe cases, was controlled by relatively small doses of ACTH; i.e., 10 to 12.5 mg. of ACTH (Armour) q.6.h.

In contrast, long standing and very severe cases did not respond fully from an arthritic point of view at even much higher doses, i.e., 25 mg. of ACTH (Armour) q.6.h.

In contrast to the arthritic symptoms, psoriatic lesions of the skin appear to require much larger doses of ACTH to effect their disappearance, and doses of 25 mg., and even 50 mg. q.6.h. have been required to obtain a complete clearing of the skin. However, even at this dosage schedule the skin lesions in long standing cases with severe nail changes are not completely reversed.

On the basis of information to date it appears that such long standing cases are not satisfactory patients for treatment with ACTH for two reasons:

a) The long continued high dosage required.
b) The lack of complete reversal.

Furthermore, all such cases appear to require a large maintenance dose to avoid relapse, and such large doses should not be considered in chronic administration studies because of the marked metabolic shifts that may occur.

On the other hand, several acute cases of simple psoriatic skin disease of relatively short duration have responded well to a dosage schedule of 25 mg. q.6.h. and the skin lesions were completely healed in a matter of ten days to two weeks. Afterwards, the dosage was tapered in the manner outlined above and some of these patients have remained in complete remission for a period of months to over a year.

7. ACUTE INFLAMMATORY DISEASES OF THE INTESTINAL MUCOSA

A. Ulcerative Colitis.

Most of the cases of ulcerative colitis studied to date have been long-standing severe cases. Bauer (38) treated one long-standing severe ulcerative colitis case and one acute ulcerative case with large doses of ACTH (25 - 50 mg. ACTH ARMOUR) q.6.h.) with a rapid disappearance of diarrhea but without a concurrent reversal of the intestinal mucosa to normal. Randolph has treated several ulcer- (39) ative colitis cases with first 25 mg. q.6.h. and then 25 mg. q.12.h. with good symptomatic relief. The interesting point with respect to these cases is the fact that the patients remained symptom-free for a substantial period of time. Dolkart (40) has treated one extremely severe ulcerative colitis case on 25 mg. q.6.h. for a two-week period, after which the dose was tapered along the lines outlined earlier and, as was the case of the patients studied by the other investigators, the symptom-free period has extended for a considerable period beyond the cessation of ACTH administration.

In view of the rapid relief of symptoms of this disabling disease, it appears worthwhile to consider the therapy of this disease with ACTH, particularly in the earlier cases before the intestinal mucosa is so seriously deranged.

In view of the fact that relatively few studies have been done on early less severe ulcerative colitis, and the fact that earlier less severe cases of other diseases may require smaller doses than long-standing severe cases, we recommend that such cases be started on 12.5 mg. ACTH (Armour) q.6.h., and if symptoms are controlled at this dosage level it should be continued until the intestinal mucosa approaches normal, after which the dose should be tapered as outlined above.

We do not recommend the use of ACTH in severe long-standing cases of ulcerative colitis unless full cognizance is taken of the metabolic and physiologic alterations that occur at high dose levels of ACTH, and unless adequate facilities are available to follow these alterations to protect the patient from over-stimulation.

B. Regional Enteritis.

In view of the fact that ACTH (Armour) appears to have an effect on ulcerative colitis, it was logical to explore the effect of this hormone in regional enteritis and in line with expectations, it has been reported to us by several investigators that the pain, cramps and diarrhea that may occur in this syndrome are brought rapidly under control in most cases. The dosage used in this disease has been 25 mg. q.6.h. of ACTH (Armour) but we recommend that a lower dosage schedule be instituted first, i.e., 12.5 mg. q.6.h. to ascer-

tain if a clinical effect can be obtained and, if so, the patient should be maintained on this dose for several weeks before tapering the dose to ascertain if a remission can be maintained.

If a symptomatic effect is not obtained after several days, the dose should be increased to 15 mg. q.6.h. for several days and, finally, to 20 or even 25 mg. if an effect is not obtained at the lower dosage level. If the higher dosage schedules are undertaken, an attempt should be made to cut back the dose after several days of asymptomatic treatment, until the dose of 10 to 12.5 mg. q.6.h. is obtained and the patient maintained on this dosage schedule for several weeks before tapering the dose further. Most of the patients studied to date have remained in remission for a considerable period of time subsequent to cessation of ACTH (Armour) administration.

C. Duodenal and Gastric Ulcers.

The patients with duodenal and gastric ulcers studied to date have done poorly on ACTH (Armour). We do not recommend it in any case having a duodenal or gastric ulcer.

8. NEPHROTIC SYNDROME

Farnsworth (41) first reported that administration of ACTH (Armour) to nephrotic children at the dose level of 25 mg. q.6.h. for 5 days resulted in retention of fluids and electrolytes during the period of ACTH administration, but that when the ACTH administration was stopped, about half of the patients diuresed not only the fluid and electrolytes retained during the period of study, but also previously retained fluids. Some patients became essentially edema free for a variable period of time with the blood chemical changes returning toward normal levels. Riley (42) has confirmed Farnsworth's observations in general and Janeway et al (43) has reported similar results on the administration of 20 to 25 mg. ACTH (Armour) every 6 hours for a period of 10 days, and on this dosage schedule they found that many of the children started diuresing while still on ACTH.

(44)

As a result of more extensive studies, Farnsworth has found that the administration of ACTH (Armour) is more effective if continued for a longer period of time and she now recommends treatment for 12 days on the following dosage schedule, which she has computed on a corrected body weight basis after making allowance for the factor of edema:

Under 50 pounds:	15 mg. every 6 hours for 12 days
50 - 75 pounds:	20 mg. every 6 hours for 12 days
76 - 100 pounds:	25 mg. every 6 hours for 12 days
100 - 150 pounds:	40 mg. every 6 hours for 12 days.

If edema increases disturbingly during this early part of treatment, administration of ACTH may be discontinued after 6 days. If diuresis fails, a second course may be reinstituted after a pause of 6 days, and the second course should be of 12 days duration, if possible.

Should diuresis occur during the first or second course, the total daily dose should be tapered slowly by a reduction in the individual dose by 1/4 at several day intervals. This may be done even if the treatment course is extended beyond the 12-day period.

In general, younger children without evidence of other renal damage have done better than older children with such evidence of other renal damage. Furthermore, some younger children have gone into complete clinical and laboratory remission of the disease and have maintained it longer than older children with longer-standing disease.

ACTH (Armour) should be used carefully in very edematous children and the cases should be on a low salt, high potassium intake and the cardiac reserve should be watched carefully since there may be increase of retention of electrolytes and fluid before diuresis occurs.

9. BLOOD DISEASES

A. Acute Leukemia.

Farber et al, (45), Pearson et al, (46), Pierce (47), Wintrobe (48), and others, have reported on the use of ACTH (Armour) in acute leukemia in both adults and children. On a dose of approximately 25 mg. q.6.h. in adults and 10 to 12.5 mg. q.6.h. in children, approximately one-half of the patients studied went into a complete clinical and hematological remission while on ACTH. The other half of the patients did not respond in any way to even excessive doses, 50 + mg. q.6.h.

Unfortunately, all of the cases that have gone into remission while on ACTH (Armour) have relapsed either while still on ACTH or after ACTH administration is stopped, and the high majority of the responding patients are unresponsive to subsequent therapy.

In view of the very short remissions observed to date and the unresponsiveness to subsequent ACTH therapy, we do not recommend the use of ACTH (Armour) in this disease syndrome. Studies are in progress regarding the combined use of ACTH and anti-folic and other chemical agents, but it is too early to assess the results obtained and we do not recommend this course of action at this time.

B. Chronic Lymphomas.

Pearson et al (49), and several other investigators have studied the effect of ACTH on the chronic lymphomas, including chronic lymphatic leukemia, chronic lymphosarcoma, Hodgkin's disease, and others. During the period of investigation there was a rapid regression of the lesions in all of these diseases on doses of 25 mg. ACTH (Armour) q.6.h., but the underlying pathologic process was not changed during the period of the study. Furthermore, the lesions rapidly return when ACTH therapy is stopped. Since the underlying pathologic process has not changed in this disease syndrome, we do not recommend the use of ACTH (Armour) in these diseases at this time.

C. Multiple Myeloma.

Thorn et al, (50), Rawson et al, (51), and several other investigators have administered ACTH to cases of multiple myeloma. In about one-half of the cases studied to date a complete remission has been obtained under ACTH (Armour) therapy at a level of 25 mg. q.6.h., whereas the other responded not at all. The remissions appear to last longer than in the case of the leukemias but it is still too early to recommend its use in this disease which requires further study, both from the point of view of interval treatment and maintenance therapy.

D. Early Aplastic Anemia.

Several cases of apparent early aplastic anemia resulting from chemical toxicity have responded while on ACTH therapy at a dose of 25 mg. q.6.h. in adults and 12.5 mg. q.6.h. in children, and most of these cases have remained in remission when ACTH therapy is stopped, providing the patient is not exposed thereafter to a toxic agent. In reactive cases, the clinically effective dose should be maintained until the blood picture and bone marrow picture returns to normal, after which the dose should be tapered as outlined above.

10. NEUROMUSCULAR DISEASES

A. Myasthenia Gravis.

First Soffer,[52] and since, Wolff and Torda,[53] have reported a substantial improvement in cases of myasthenia gravis after 5 days of treatment with ACTH (Armour) administered 25 mg. q.6.h. No improvement occurs while the hormone is being administered, but the majority of cases studied to date have improved markedly and remained improved for subsequent periods of time subsequent to the ACTH therapy. This disease requires further investigation in specialized facilities and ACTH is not recommended in this disease at this time.

B. Progressive Muscular Dystrophy.

Progressive muscular dystrophy has been studied and there has been no effect on the course of the disease in any of the cases studied to date and we, therefore, do not recommend ACTH (Armour) in this disease syndrome.

C. Progressive Muscular Atrophy.

Cases of this disease syndrome have been studied with no detectable effect and we, therefore, do not recommend ACTH (Armour) in this disease.

11. MENTAL DISEASES

The only mental disease in which results to date suggest a use for ACTH is in anorexia nervosa, and here the main purpose is to increase the appetite of the patient and improve the nutrition accordingly, and to allow psychiatric evaluation of the problems underlying the syndrome.

Thorn, et al,(54) have found that 10 mg. q.6.h. is very effective in improving the appetite of the patient and in attaining a weight gain and they have also found that the patients have been much more responsive to psychiatric analysis and treatment.

12. MISCELLANEOUS

ACTH has been used in a number of other conditions, but it is as yet too early to recommend its use pending further clinical evaluation. However, it has been shown by Steinbrocker (55), Thorn (56) and others, that the pain and inflammatory reaction in degenerative arthritis or osteoarthritis can be kept under full control by ACTH administration. It is doubtful, however, that the underlying disease process is substantially altered. Nonetheless, small doses of ACTH (Armour), i.e., 5 to 10 mg. q.6.h. or q.8.h., or even less, may control the pain and inflammatory reaction in this disease syndrome.

13.

The contraindications outlined in the previous section of this booklet should be kept fully in mind at all times in the use of ACTH, and these are listed as follows for this purpose -

Hypertension
Diabetes Mellitus
Chronic Nephritis
Known Psychotics and Psychopathic Personalities
Cushing's Syndrome
Congestive Heart Failure
Hirsutism

For detail, see "General Principles to be Considered in Using Acth."

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